/ Review

Phosphine Oxide-Catalyzed Asymmetric Aldol Reactions and Double Aldol Reactions

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Chiral phosphine oxides successfully catalyze asymmetric *cross*-aldol reactions of various carbonyl compounds in a highly enantioselective manner. The phosphine oxide catalysts coordinate to chlorosilanes to form chiral hypervalent silicon complexes *in situ*, which activate both aldol donors and acceptors, thus realizing *cross*-aldol reactions between a ketone and an aldehyde, between two aldehydes, between two ketones, and of 2,6-diketones. The use of phosphine oxide catalysis can be further extended to achieve the first catalytic enantioselective double aldol reactions, realizing one-pot stereoselective construction of up to four stereogenic centers.

Key words aldol reaction; phosphine oxide; tandem catalysis; hypervalent silicon complex; stereoselective; sequential activation

1. Introduction

The asymmetric aldol reaction is one of the most powerful and common transformation reactions that contribute greatly to the fields of pharmaceuticals and agricultural chemicals.^{1–4)} In particular, ever since the catalysis of the aldol reaction of fructose derivatives in the human body by the glycolytic enzyme *aldolase* was reported, asymmetric aldol reactions have garnered considerable research attention in the pharmaceutical sciences.⁵⁾ Remarkable progress has been achieved in terms of stereocontrol and direction control by developing the Mukaiyama aldol reaction^{6,7)} or the Evans aldol reaction.⁸⁾ Asymmetric *cross*-aldol reactions of different carbonyl compounds in the presence of bimetallic catalysts reported by Shibasaki and colleagues,^{9,10)} as well as the discovery of a proline catalyst by Barbas and List,^{11–13)} have accelerated the development of catalytic asymmetric direct *cross*-aldol reactions in the last two decades.^{14–17)}

Lewis base-catalyzed aldol reactions of trichlorosilyl enol ethers^{18–20)} were pioneered by Denmark *et al.*, who used a chiral phosphoramidate to form a chiral hypervalent silicon complex, which facilitated asymmetric aldol reactions in a highly diastereo- and enantioselective manner.^{21–27)} Our group has reported chiral pyridine *N*-oxides²⁸⁾ and bisphosphine oxides^{29,30)} as catalysts for aldol reactions of trichlorosilyl enol ethers, thus extending the utility of these in organic synthesis. A chiral hypervalent silicon complex, formed from (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) dioxide

(BINAPO) and trichlorosilyl enol ether, has a strongly electrophilic Si atom and strongly nucleophilic adjacent ligands³¹⁾ (Chart 1). Stereoselective coordination of an aldehyde oxygen

Chart 1. Phosphine Oxide-Catalyzed Aldol Reaction

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atom to the chiral hypervalent Si complex facilitates C–C bond formation *via* a six-membered transition state, providing an aldol adduct with high diastereoselectivity, as reflected by the *E/Z* ratio of the trichlorosilyl enol ethers, as well as high enantioselectivity. The chiral catalyst then dissociates from the Si atom furnishing a trichlorosilylated product, and then participates in the next catalytic cycle.

Although Lewis base-catalyzed aldol reactions provide β -hydroxycarbonyl compounds in a highly diastereo- and enantioselective manner, a two-step preparation has been required to obtain the trichlorosilyl enol ethers from the carbonyl compounds. To increase the efficiency and utility of the Lewis base-catalyzed aldol reactions, we envisaged an *in-situ* preparation of trichlorosilyl enol ethers from carbonyl compounds. In this review, we would like to introduce the sequential formation of hypervalent Si complexes, achieving a variety of catalytic asymmetric *cross*-aldol reactions. Furthermore, sequential phosphine oxide catalysis has been extended to the first catalytic enantioselective double aldol reactions, thus realizing the rapid synthesis of various natural products and molecular skeletons with multiple stereogenic carbon centers.

2. Asymmetric *cross*-Aldol Reactions between Carbonyl Compounds with Chiral Hypervalent Silicon Complexes

We initially examined the direct conversion from a mother ketone to a trichlorosilyl enol ether by treatment with silicon tetrachloride and an amine base, based on the reported synthesis of trialkylsilyl enol ethers from ketones and trialkylsilyl bromide or iodide in the presence of amines.³²⁾ However, no conversion to trichlorosilyl enol ethers occurred because of the lower silylating ability of silicon tetrachloride. Since the formation of hypervalent silicon complexes with a Lewis base increased the electrophilicity and Lewis acidity of the Si atom, use of a chiral phosphine oxide, (*S*)-BINAPO, was investigated next. As expected, the phosphine oxide catalyst successfully promoted the *in situ* formation of trichlorosilyl enol ether from ketone **1**, and the subsequent addition of aldehyde **2** afforded the aldol adduct **3** in moderate yield and stereoselectivity (Chart 2). This result indicates that the phosphine oxide sequentially formed hypervalent Si complexes with silicon tetrachloride and trichlorosilyl enol ether to activate the aldol donor and acceptor, respectively, facilitating the formation of the aldol adduct.³³⁾ Trichlorosilyl triflate³⁴⁾ mediated the formation of trichlorosilyl enol ethers at -40°C , resulting in higher stereoselectivities.³⁵⁾

We next conducted enantioselective aldol reactions of vari-

Chart 2. Phosphine Oxide-Catalyzed *cross*-Aldol Reaction *via* the Sequential Formation of Hypervalent Si Complexes

ous ketones and aldehydes under optimal conditions (Table 1). Trichlorosilyl triflate was able to successfully promote the enolization of an acyclic ketone propiophenone (**6**) to predominantly form a *Z*-enol ether, producing the *syn*-adduct **7** as the major isomer in 71% yield with 83% enantiomeric excess (ee) (entry 2). Cyclohexanone derivatives **8** and **10** also showed high stereoselectivity (entries 3 and 4). Although an α,β -unsaturated aldehyde **12** showed lower reactivity than aromatic aldehydes, good stereoselectivity was maintained (entry 5). 2-Naphthaldehyde (**14**) gave the corresponding aldol adduct **15** in 79% yield with high diastereo- and enantioselectivity (entry 6), while *para*-bromobenzaldehyde (**16**) bearing an electron-withdrawing substituent resulted in higher enantioselectivity (88% ee) (entry 7).

Although aldol reactions between aldehydes are classically developed C–C bond forming reactions, catalytic asymmetric *cross*-aldol reactions between two different aldehydes are rare, due to unfavorable side reactions such as self-aldol reactions and dehydration.^{36–40)} The hypervalent silicon complex successfully mediated the *cross*-aldol reaction between aliphatic aldehydes and aromatic aldehydes.³³⁾ Aliphatic aldehydes have low reactivity as aldol acceptors because of the formation of trichlorosilylated chlorohydrins in the reaction media.⁴¹⁾ Therefore, aliphatic isobutyraldehyde (**18**) was chemoselectively enolized to form the trichlorosilyl enol ether, which would then undergo a *cross*-aldol reaction with aromatic aldehyde **19**. Although stereoselectivity remained unsatisfactory, the reaction proceeded smoothly to yield the *cross*-aldol adduct **20** without any self-aldol or dehydration products (Chart 3).

In order to construct tetrasubstituted stereogenic carbon centers using an aldol reaction, the ideal aldol acceptors are

Biography

Shunsuke Kotani was born in 1980 in Gunma, Japan, and received his B.S. (2003) and M.S. (2005) degrees from Hokkaido University under the guidance of Professor Shunichi Hashimoto. He completed his doctoral studies under the supervision of Professor Makoto Nakajima at Kumamoto University in March 2008. He then moved to the University of California, Irvine, as a JSPS postdoctoral fellow in the group of Professor Scott. D. Rychnovsky. In 2009, he began his academic career at Kumamoto University, where he was promoted to associate professor in 2014. He has received the Pharmaceutical Society of Japan Award for Young Scientists (2018). His research interests include the invention of new reactions and stereocontrol in carbon–carbon coupling.

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Table 1. Phosphine Oxide-Catalyzed Aldol Reaction with Trichlorosilyl Triflate

$ \begin{array}{c} \text{ketone} \\ \text{(1.5 eq)} \end{array} + \text{ArCHO} \xrightarrow[\text{EtCN, } -40^\circ\text{C, 2 h}]{\begin{array}{l} (S)\text{-BINAPO (10 mol \%)} \\ \text{SiCl}_3\text{OTf (2.0 eq)} \\ \text{Cy}_2\text{NMe (10 eq)} \end{array}} \begin{array}{c} \text{Product} \end{array} $						
Entry	Ketone	Aldehyde	Product	Yield, %	<i>anti</i> / <i>syn</i> ^a	ee, % (<i>anti</i>) ^b
1		PhCHO (2)	5	76	93 / 7	83
2 ^c		2	7	71	27 / 73	83 ^d
3 ^e		2	9	81	97 / 3	82
4		2	11	82	97 / 3	83
5 ^f	10	PhCH=CHO (12)	13	65	93 / 7	77
6	10	2-naphthaldehyde (14)	15	79	97 / 3	83
7 ^f	10	4-Br-C ₆ H ₄ CHO (16)	17	84	97 / 3	88

a) Determined by ¹H-NMR. b) Determined by HPLC analysis. c) The reaction mixture was stirred for 3 h before addition of **2**. d) Ee of *syn*-isomer. e) SiCl₃OTf was added last. f) The reaction was continued for 4 h.

Chart 3. Phosphine Oxide-Catalyzed *cross*-Aldol Reaction between **18** and **19** Chart 4. Asymmetric *cross*-Aldol Reactions between **21** and **22**

ketones.⁴²⁾ The catalytic asymmetric aldol reaction between two simple ketones is challenging because of the lower electrophilicity and more difficult enantiofacial selection of ketones compared to those of aldehyde acceptors.^{43–47)} In direct aldol reactions between two simple ketones, both can function as aldol donors and acceptors; therefore, a precise recognition

Chart 5. Asymmetric *cross*-Aldol Reaction between Two Different Simple Ketones

of the aldol donor and acceptor in the reaction medium is essential. Tanabe and colleagues reported the *cross*-aldol reaction of two simple ketones *via* a titanium enolate intermediate produced by a stepwise procedure.^{48–51)} We envisaged that the extremely strong silylating ability of trichlorosilyl triflate would enable the complete conversion of ketones to the corresponding trichlorosilyl enol ethers, thus facilitating the *cross*-aldol reaction between two simple ketones.³⁵⁾ First, a trichlorosilyl enol ether was prepared by treating acetone (**21**) with

Fig. 1. Asymmetric Sequential Aldol Reactions

Table 2. Asymmetric Intramolecular Aldol Reaction

Regioselective Enolization

Entry	Diketone, R	Product	Yield, %	ee, % ^{a)}
1	Ph (31)	32	82	91
2	4-Cl-C ₆ H ₄ (33)	34	86	96
3	4-MeO-C ₆ H ₄ (35)	36	86	90
4	2-Naphthyl (37)	38	83	92
5	PhCH ₂ CH ₂ (39)	40	77	87
6	CH ₂ =CHCH ₂ CH ₂ (41)	42	75	87

^{a)} Determined by HPLC analysis.

trichlorosilyl triflate and *N,N*-diisopropylethylamine, and then acetophenone (**22**) was loaded into the reaction mixture (Chart 4). The asymmetric *cross*-aldol reaction occurred cleanly and smoothly to yield adduct **23** in 85% yield with 74% ee. Changing the addition order of these ketones produced the other *cross*-aldol adduct **24** in 75% yield.⁵²⁾

Cross-aldol reactions between various types of ketones were conducted using the (*S*)-BINAPO catalyst (Chart 5). The methyl ketone moiety of 2-butanone was predominantly enolized and then reacted with acetophenone to produce the *cross*-aldol adduct **25** in 65% yield with 74% ee. The reaction of cyclohexanone (**4**) as the aldol donor with various ketones afforded adducts **24–30** with good-to-high diastereoselectivity. Although acetophenone derivatives gave the same level of reactivity and enantioselectivity, propiophenone (**6**) resulted in decreased reactivity and diastereoselectivity. Benzylacetone, bearing a small steric difference between the two substituents, reacted well to provide good diastereo- and enantioselectivity.⁵²⁾

As described above, the use of trichlorosilyl triflate realized asymmetric *cross*-aldol reactions between two ketones in a stepwise manner. However, the stepwise procedure is not applicable to the intramolecular aldol reaction. Furthermore, the β -hydroxycycloalkanones produced are dehydrated to the corresponding 2-cycloalkenones more readily than acyclic β -hydroxycarbonyl compounds. Therefore, there have been few reports of asymmetric preparations of β -hydroxycycloalkanones using intramolecular aldol reactions of diketones.^{53,54)} Based on our background in Lewis base-catalyzed aldol reactions, we predicted that the trichlorosilyl moiety in the aldol product would suppress dehydration of the aldolate. Furthermore, a sterically congested hypervalent silicon complex formed by chiral phosphine oxide should recognize the smaller alkyl ketone moiety, promoting regioselective enolization (Table 2). When diketone **31** was treated with silicon tetrachloride and *N,N*-diisopropylethylamine in the presence of a (*S*)-TMS₂-BINAPO catalyst,^{55,56)} the β -hydroxycyclohexanone derivative **32** was obtained in 82% yield with 91% ee. The hypervalent silicon complex also efficaciously mediated the intramolecular aldol reaction of 2,6-diketones to give β -hydroxycyclohexanones in high yield and with high enantioselectivity.⁵⁷⁾

3. Asymmetric Double Aldol Reactions Catalyzed by Chiral Phosphine Oxides

The aldol reaction sequence provides an effective synthetic methodology for polyol and polyketide derivatives, which are found in many medicines as well as in biologically active natural products. Therefore, the one-pot sequential stereoselective aldol reaction allows us to access these derivatives. In 1999, the first example of a stereoselective sequential aldol reaction was shown by Abiko *et al.*, who demonstrated that an acetic acid ester bearing a chiral auxiliary and an aldehyde gave a double aldol adduct with high diastereoselectivity^{58–61)} (Fig. 1-a). Yamamoto and colleagues reported that the tris(trimethylsilyl)silyl (super-silyl) enol ether undergoes a triple aldol reaction^{62–65)} (Fig. 1-b) in a highly *syn*-selective manner, due to the strong steric effect of the super-silyl group.

Fig. 2. Sequential Mechanism of Phosphine Oxide-Catalyzed Double Aldol Reactions

Chart 6. Phosphine Oxide-Catalyzed Double Aldol Reactions of Acetophenone and Benzaldehyde

In 2015, Kanai and Matsunaga's group developed the quadruple aldol reaction of enol boronate catalyzed by a chiral copper complex⁶⁶⁾ (Fig. 1-c). Recent progress in sequential asymmetric aldol reactions *via* various approaches has been demonstrated, which enabled us to synthesize a variety of polyols and polyketides. In this chapter, we describe the further extension of phosphine oxide catalysis to develop the first catalytic enantioselective double aldol reactions and other related reactions.

In the above-mentioned Lewis base-catalyzed aldol reactions, chiral hypervalent silicon complexes promoted the formation of trichlorosilyl enol ethers and the subsequent asymmetric *cross*-aldol reactions with various carbonyl compounds in a highly enantioselective manner. Since the silyl aldolate intermediate produced in the aldol reaction is also a carbonyl compound, it is possible for it to undergo a second aldol reaction, resulting in a catalytic asymmetric double aldol reaction (Fig. 2).

We initially examined the reaction between ketone **22** and aldehyde **2** in the presence of (*S*)-BINAPO, silicon tetrachloride, and *N,N*-diisopropylethylamine in dichloromethane at -40°C (Chart 6). The reaction furnished the double aldol adduct **43** in 90% yield with good diastereo- and enantioselectivity (dr 81/19, 60% ee (major)). This is the first report of catalytic enantioselective double aldol reactions of carbonyl compounds.⁶⁷⁾ The hypervalent silicon complex activates the silyl aldolate to generate bis(trichlorosilyl)enol ether in the reaction media, which undergoes a second aldol reaction with an aldehyde to furnish the double aldol adduct. In the transformation, phosphine oxide formed several hypervalent silicon complexes to mediate the sequential reaction. Reactions using various aryl methyl ketones and aldehydes afforded the corresponding double aldol adducts with good-to-high stereoselectivity (Table 3).

In the double aldol reaction of 2-alkanones, the second enolization did not occur at the same α -position of the carbonyl moiety as the first enolization, but rather, at the other α -position to furnish 1,5-dihydroxy-3-pentanones (Chart 7).

Table 3. Phosphine Oxide-Catalyzed Double Aldol Reaction of Aryl Methyl Ketones

$\text{R}^1\text{C(=O)CH}_3 + \text{R}^2\text{CHO}$ (2.2 eq)		$\text{R}^1\text{C(=O)CH}_3 + \text{R}^2\text{CHO}$ (2.2 eq)		$\text{R}^1\text{C(=O)CH}_3 + \text{R}^2\text{CHO}$ (2.2 eq)		
Entry	Ketone, R ¹	Aldehyde, R ²	Product	Yield, %	dr ^{a)}	ee (major), % ^{b)}
1	Ph (22)	Ph (2)	43	86	78/22	70
2 ^{c)}	4-Br-C ₆ H ₄ (44)	2	45	78	77/23	75
3 ^{d)}	PhCH=CH (46)	2	47	87	83/17	84
4 ^{d)}	Cyclohexyl (48)	2	49	71	77/23	71
5	2-Furyl (50)	2	51	88	86/14	91
6 ^{d)}	Cyclopropyl (52)	2	53	77	98/2	93
7 ^{d)}	52	4-Me-C ₆ H ₄ (54)	55	90	97/3	91
8 ^{d)}	52	16	57	93	97/3	90
9 ^{d)}	52	12	59	61	80/20	85
10	50	2-Furyl (60)	61	80	92/8	97

a) Determined by ¹H-NMR. b) Determined by HPLC analysis. c) Reaction continued for 48 h. d) In CH₂Cl₂ instead of in CH₂Cl₂/EtCN.

This reaction produced up to three stereogenic centers from simple 2-alkanones and aldehydes in a single operation (Table 4). The reaction of acetone (**21**) provided a C₂-symmetrical adduct, **75**, as the only diastereomer with 91% ee without undergoing dehydration (entry 9).⁶⁸⁾

The above-described methodology was applied to the total synthesis of (–)-ericanone (**76**), which should have antioxidant or antitumor activity due to its similarity to members of the curcuminoid families.^{69,70)} The double aldol reaction of **21** with 4-nosyloxybenzaldehyde (**77**) furnished the double aldol adduct **78** in 94% yield with 98% ee in the presence of the originally designed (*S*)-TIPS₂-BINAPO (Chart 8). Removal of the nosyl groups, followed by reduction of the double bonds, afforded (–)-ericanone.⁷¹⁾

The hypervalent silicon complex formed from silicon tetrachloride was able to mediate the double aldol reaction of 2-alkanones in a highly stereoselective fashion. However, other ketones, such as diethyl ketone, did not undergo any double aldol reaction because silyl enol ethers were not generated in the first aldol reaction due to the low silylating ability of the hypervalent silicon complex. Therefore, we used trichlorosilyl triflate, instead of silicon tetrachloride, for the double aldol reaction, and were able to obtain the desired adduct with high diastereo- and enantioselectivity. Fortunately, the double aldol reaction of symmetric ketones gave C₂-symmetric 2,4-disubstituted 1,5-dihydroxy-3-pentanone derivatives in a single

Chart 7. Reaction Pathway of the Double Aldol Reaction of 2-Alkanones

Chart 8. Total Synthesis of (-)-Ericanone

Chart 9. Double Aldol Reaction/Cyclization Reaction of 4-Methoxy-3-buten-2-one (**96**)

Table 4. Phosphine Oxide-Catalyzed Double Aldol Reaction of Ketones with Silicon Tetrachloride

$\text{R}^1\text{CH}_2\text{COCH}_3 + \text{ArCHO} \xrightarrow[\text{CH}_2\text{Cl}_2/\text{EtCN}, -60^\circ\text{C}, 24\text{ h}]{(S)\text{-BINAPO (10 mol \%)}, \text{SiCl}_4 (4.0\text{ eq}), \text{Cy}_2\text{NMe (5.0 eq)}} \text{ArCH(OH)CH(R}^1\text{)CH}_2\text{CH(OH)Ar}$					
Entry	Ketone, R ¹	Aldehyde, Ar	Product	Yield, %	dr ^{a)} ee (major), % ^{b)}
1	Me (62)	2	63	86	90/10 91
2	Et (64)	2	65	87	90/10 95
3	ⁿ Pr (66)	2	67	86	89/11 94
4	Me ₂ C=CHCH ₂ (68)	2	69	84	89/11 91
5	64	16	70	89	90/10 92
6 ^{c)}	64	19	71	66	92/8 98
7	64	54	72	76	91/9 97
8	64	4-NO ₂ -C ₆ H ₄ (73)	74	56	92/8 80
9 ^{d)}	21	2	75	84	— 91

a) Determined by ¹H-NMR. b) Determined by HPLC analysis. c) Reaction continued for 48 h. d) Reaction was conducted with ^tPr₂NEt in place of Cy₂NMe in CH₂Cl₂ at -60 °C.

Table 5. Phosphine Oxide-Catalyzed Double Aldol Reaction of 2-Alkanones with Trichlorosilyl Triflate

Entry	Ketone	R ¹	R ²	Aldehyde R ³	Temp, °C	Product	Yield, % ^{a)}	dr ^{b)}	ee, % ^{c)}
1	79	Me	Me	2	−40	80	86	95/5	96
2	79	Me	Me	54	−40	81	79	96/4	97
3	79	Me	Me	19	−30	82	85	95/5	98
4	79	Me	Me	16	−20	83	79	90/10	97
5	79	Me	Me	14	−40	84	79	98/2	98
6	79	Me	Me	12	−30	85	66	94/6	98
7	86	Et	Et	2	−30	87	71	92/8	97
8	88	ⁿ Pr	ⁿ Pr	2	−30	89	64	93/7	99
9	90	Bn	Bn	2	−30	91	72	93/7	99
10	92	Me	Et	2	−30	93	71	90/10	97
11	94	Me	ⁿ Pr	2	−30	95	70	90/10	97

a) Isolated yield of major isomer. b) Determined by the isolated product or ¹H-NMR. c) Determined by HPLC analysis.

step, while unsymmetrical ketone **94** afforded a more sterically congested molecule **95** bearing four stereogenic centers (Table 5). The enantioselective double aldol reaction could be used to prepare chiral stereopentad precursors in good yield with high enantioselectivity.⁷²⁾

The double aldol reaction of aryl methyl ketones produced optically active 2-acyl-1,3-diols bearing two stereogenic centers with high enantioselectivity. We envisaged that the double aldol products, generated from β-alkoxyenones, could

Chart 10. Double Aldol Reaction/Cyclization Reaction of 4-Methoxy-3-penten-2-one (**98**)

be regioselectively cyclized to obtain 2,3-dihydro-4-pyranones with three contiguous stereogenic centers. 4-Methoxy-3-buten-2-one (**96**) functioned as an aldol donor and reacted with aldehyde **2** under the reaction conditions described in Chart 9. The chiral phosphine oxide effectively facilitated the double aldol reaction of **96** with aldehyde **2**, and the subsequent regioselective cyclization afforded the corresponding highly functionalized 2,3-dihydro-4-pyranone **97** in 69% yield with good diastereo- and enantioselectivity. This method offers an alternative to the existing methods for the synthesis of 2,3-dihydro-4-pyranones from the corresponding ketones and aldehydes.⁷³⁾

To further extend the substrate scope, we studied the reaction of 4-methoxy-3-penten-2-one (**98**) (Chart 10). Interestingly, 2,6-disubstituted 2,3-dihydro-4-pyranone **99**, instead of 2,3-disubstituted 2,3-dihydro-4-pyranone, was obtained in 51% yield with high diastereo- and enantioselectivity (Chart 10). After the first aldol reaction, the amine preferably removed the proton at the γ -position to the silyl aldolate to form trichlorosilyl dienolate, and the subsequent vinylogous addition to the aldehyde, followed by cyclization, afforded the 2,6-disubstituted 2,3-dihydro-4-pyranones in a highly stereoselective manner.⁷⁴⁾

4. Conclusion

In this study, we obtained phosphine oxide catalysts that sequentially catalyzed asymmetric *cross*-aldol reactions between different carbonyl compounds *via* the formation of hypervalent silicon complexes. Moreover, enantioselective double aldol reactions have been developed for the first time, realizing the enantioselective construction of multiple stereogenic carbon centers and asymmetric syntheses of natural product (–)-ericanone and 4-pyranone derivatives. This catalytic system may now be further developed into novel activation systems using hypervalent silicon complexes, realizing chemoselective and stereoselective transformations.

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Conflict of Interest The author declares no conflict of interest.

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