Stereoselective Synthesis of Multiple Stereocenters by Using a Double Aldol Reaction

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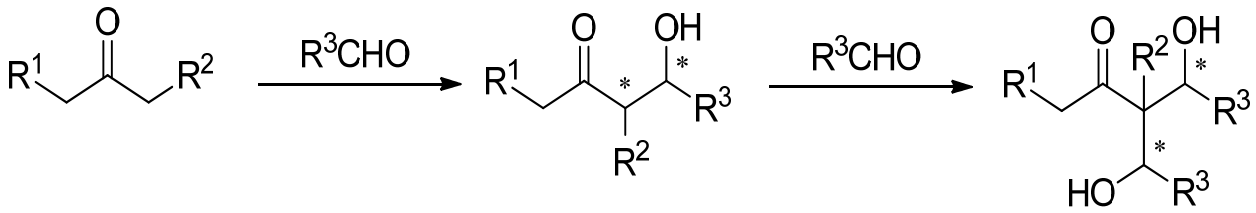
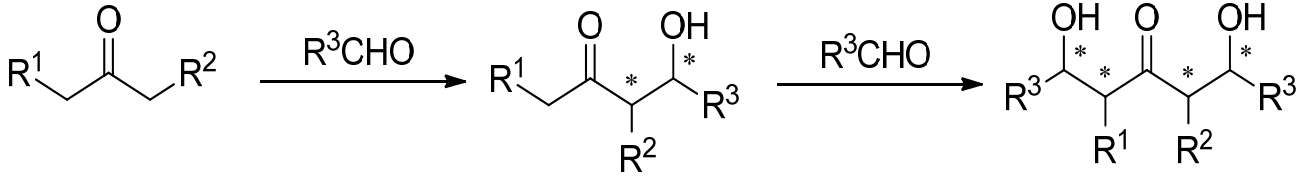
Introduction

Among the various sequential aldol reactions, double aldol reactions involving one aldol donor and two aldol acceptors have two types of reaction modes

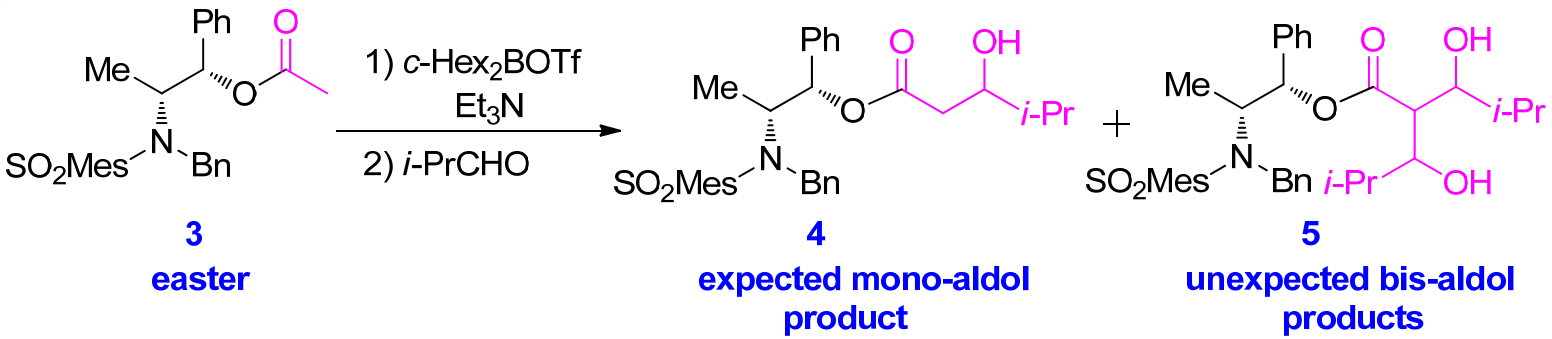
a) two aldol reactions may occur at a single *α* position on an aldol donor to give a **branched double aldol adduct** with three contiguous stereogenic centers



b) a reaction at both α-positions of a carbonyl group in an aldoldonor provides a **linear double aldol adduct** having a **1,5-dihydroxy group** with at most four chiral centers in a single operation.



Introduction



3
easter

4
expected mono-aldol product

5
unexpected bis-aldol products

In 1999, the first asymmetric double aldol reaction was reported by Masamune, Abiko, and co-workers, who used boron triflate in the reaction of a chiral ester and an aldehyde to afford a double aldol adduct diastereoselectively.

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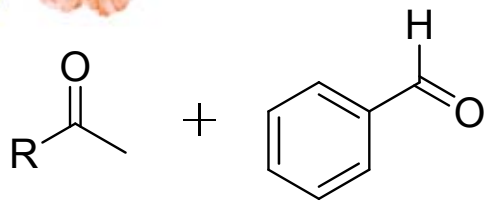
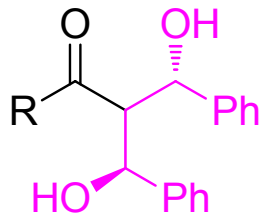
Introduction

In 2011, Makoto Nakajima developed the first enantioselective double aldol reaction using a chiral phosphine oxide as a Lewis base catalyst, thus producing double aldol adducts with high stereoselectivities.

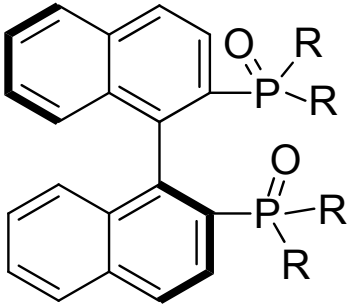


1 **2a**

(S)-BINAPO(10 mol %)
$SiCl_4$ (4 equiv)
cHex_2NMe (5 equiv)
EtCN/CH_2Cl_2
propionitrile
-60 °C



***chiro*-3**
the branched aldol adducts



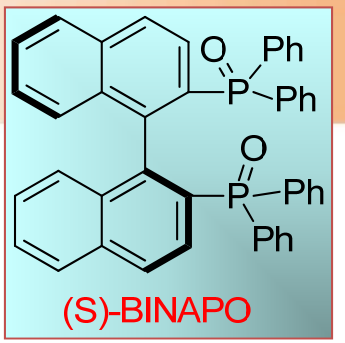
(S)-BINAPO: R=Ph

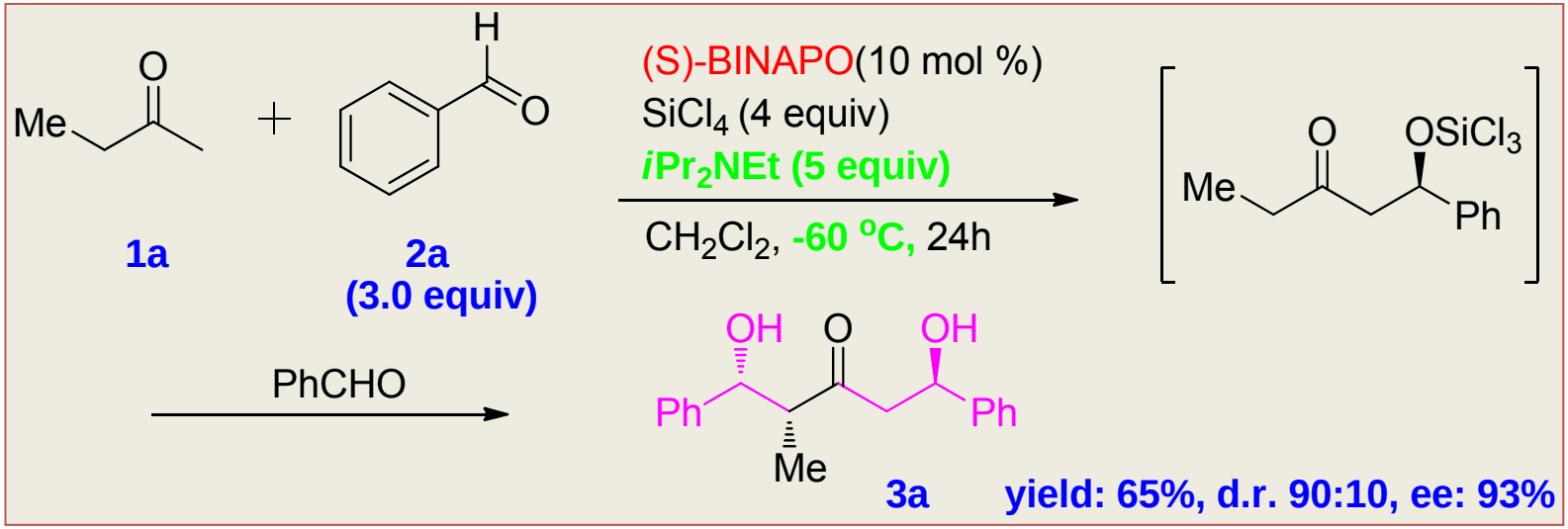
Entry	Ketone **1**	R	Product **3**	Yield [%][b]	d.r.[c]	*ee* [%] (*chiro*)[d]
1	**1a**	Ph	**3a**	86	78:22	70
2[e]	**1b**	4-BrC_6H_4	**3b**	78	77:23	75
3	**1c**	4-$MeOC_6H_4$	**3c**	88	85:15	70
4	**1d**	2-$MeOC_6H_4$	**3d**	82	90:10	56
5	**1e**	2-Naphthyl	**3e**	88	78:22	72
6[f]	**1f**	PhCH=CH	**3f**	87	83:17	74
7	**1g**	2-Thienyl	**3g**	95	91:9	84
8	**1h**	2-Furyl	**3h**	88	86:14	91
9[f]	**1i**	Cyclopropyl	**3i**	77	98:2	93

Chem. Eur. J. **2011**, 17, 7992 – 7995

Content

the first enantioselective **linear double aldol reaction** using silicon tetrachloride and a chiral phosphine oxide as an organocatalyst



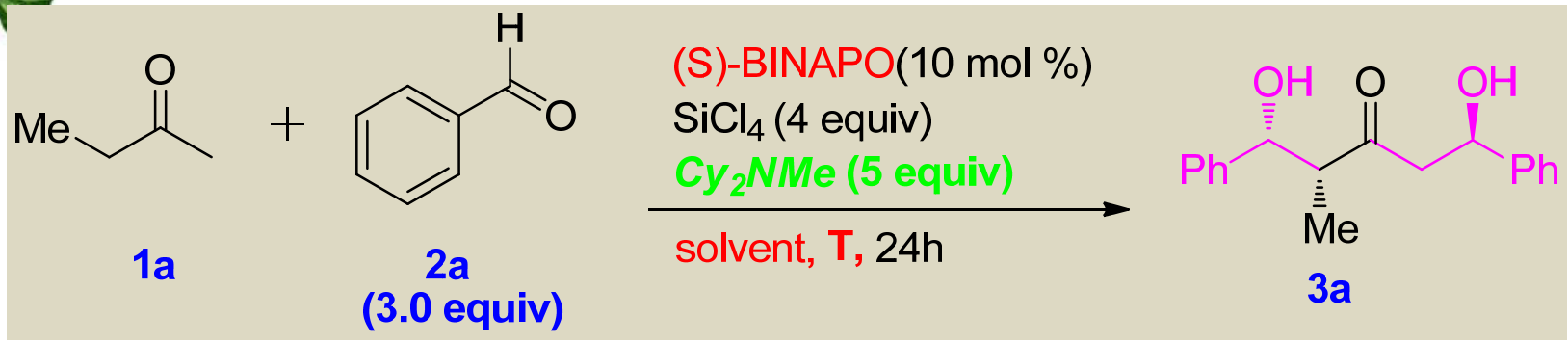


Preliminary result of the linear-type double aldol reaction.

The linear-type adduct **3a** was obtained in a 65%yield with a high diastereoselectivity (d.r.=90:10) and a high enantioselectivity (93%ee) for the major isomer.

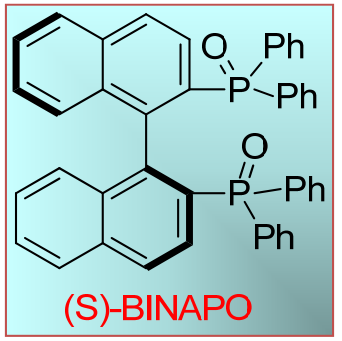
Content

To improve both the yield and selectivity, the author conducted the double aldol reaction under various reaction conditions using (S)-binapo as a Lewis base catalyst.



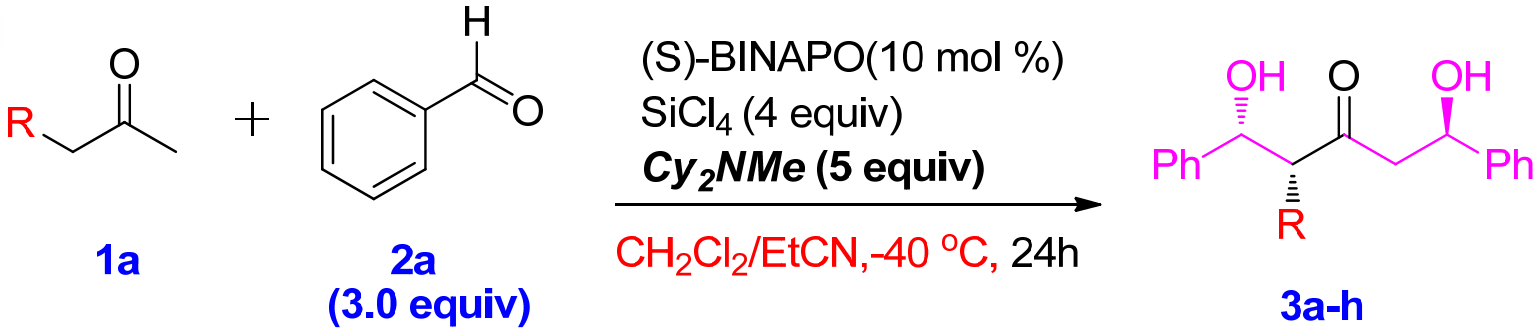
Entry	Solvent	T [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	CH_2Cl_2	−60	65	90:10	93
2	CH_2Cl_2	−60	71	91:9	95
3[f]	CH_2Cl_2	−60	73	91:9	94
4	CH_2Cl_2	−40	80	90:10	86
5	EtCN	−40	28	89:11	97
6	CH_2Cl_2/EtCN (1:1)	−40	86	90:10	91

[a] Unless otherwise noted, reactions were carried out by adding of $SiCl_4$ (2.0 mmol) to a solution of **1a** (0.5 mmol), **2a** (1.5 mmol), Cy_2NMe (2.5 mmol), and (*S*)-binapo (10 mol%) in solvent (5 mL). [b] Yield of isolated product. [c] The ratio of the major isomer to the minor isomer was determined by ^1H NMR analysis. [d] The *ee* value (major isomer) was determined by HPLC analysis. [e] iPr_2NEt was used in place of Cy_2NMe. [f] For 48 h.



Content

Double aldol reaction of various ketones (1a–h) and benzaldehyde (2a) catalyzed by (S)-binapo



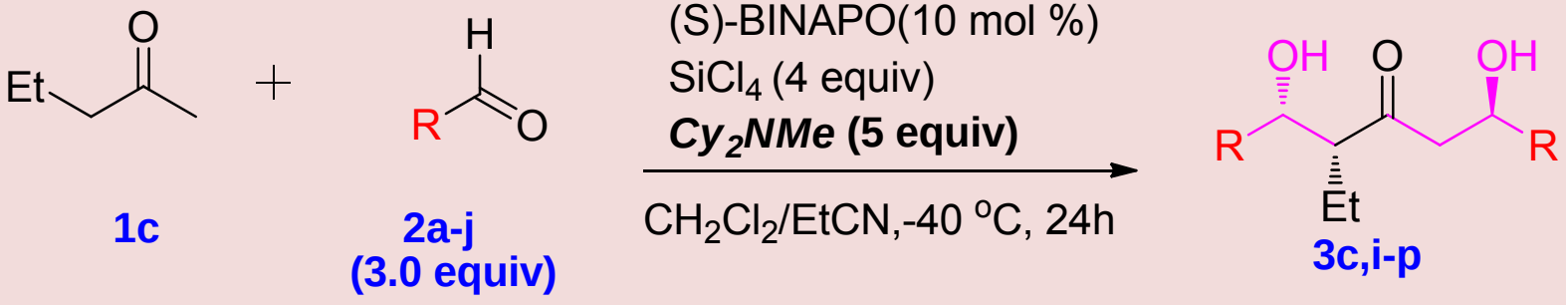
1a **2a (3.0 equiv)** **3a-h**

Entry	R (1)	3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me (1a)	3a	86	90:10	91
2[e]	H (1b)	3b	84	–	91
3	Et (1c)	3c	87	90:10	95
4	*n*Pr (1d)	3d	86	89:11	94
5	Bn (1e)	3e	69	89:11	79
6	-$CH_2CH{=}C(CH_3)_2$ (1f)	3f	84	89:11	92
7[f]	-$(CH_2)_2CO_2Et$ (1g)	3g	65 (15)[g]	89:11	94
8[f]	-$(CH_2)_3C(O)Ph$ (1h)	3h	67	90:10	81

[a] Unless otherwise noted, reactions were carried out in the presence of **1a–h** (0.5 mmol), **2a** (1.5 mmol), $SiCl_4$ (2.0 mmol), Cy_2NMe (2.5 mmol), and (*S*)-binapo (10 mol%) in EtCN (2.5 mL) and CH_2Cl_2 (2.5 mL) at −40 °C. [b] Yield of isolated product. [c] The ratio of the major isomer to the minor isomer was determined by ^1H NMR analysis. [d] The *ee* value (major isomer) was determined by HPLC analysis. [e] The reaction was conducted with iPr_2NEt in place of Cy_2NMe in CH_2Cl_2 at −60 °C. [f] For 48 h. [g] The yield of lactonized product is given within the parentheses.

Content

Double aldol reaction of 2-pentanone (1c) and various aldehydes (2a–i) catalyzed by (S)-binapo.



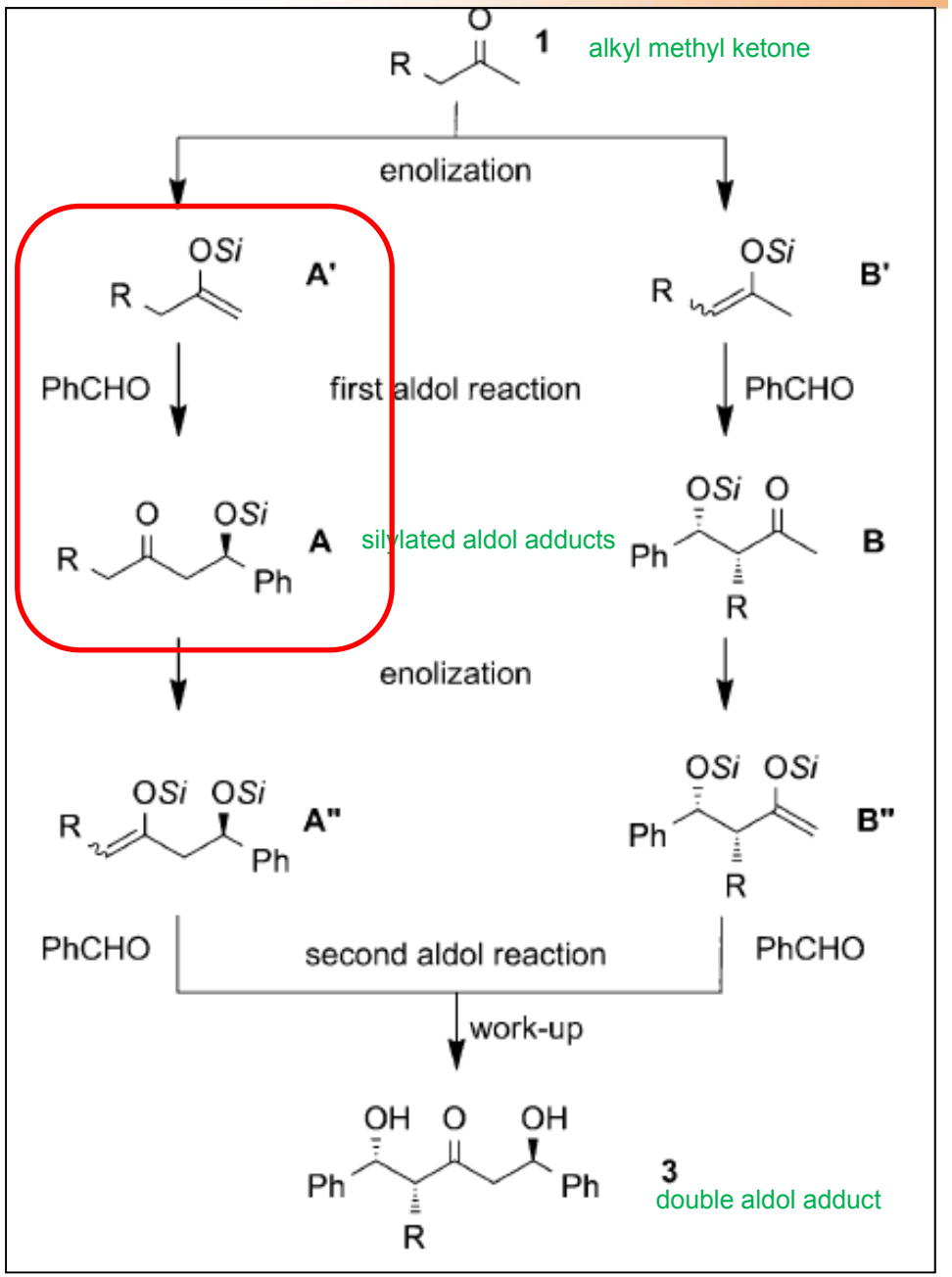
Entry	R (2)	3	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph (2a)	3c	87	90:10	95
2	4-BrC_6H_4 (2b)	3i	89	90:10	92
3[e]	4-$MeOC_6H_4$ (2c)	3j	66	92:8	98
4	4-MeC_6H_4 (2d)	3k	76	91:9	97
5[e]	3,5-$Me_2C_6H_3$ (2e)	3l	72	92:8	91
6	2-naphthyl (2f)	3m	78	90:10	93
7	1-naphthyl (2g)	3n	58	89:11	93
8	2-furyl (2h)	3o	65	90:10	88
9	2-thienyl (2i)	3p	71	92:8	95

[a] All reactions were carried out in the presence of **1c** (0.5 mmol), **2a–i** (1.5 mmol), $SiCl_4$ (2.0 mmol), Cy_2NMe (2.5 mmol), and (*S*)-binapo (10 mol%) in CH_2Cl_2 (2.5 mL) and EtCN (2.5 mL) at −40 °C. [b] Yield of isolated product. [c] The ratio of the major isomer to the minor isomer was determined by ^1H NMR analysis. [d] The *ee* value (major isomer) was determined by HPLC analysis. [e] For 48 h.

Content

Possible reaction routes of the double aldol reaction. Si=$SiCl_3$.

To investigate the first aldolization process, The author performed the reaction of 3-pentanone with benzaldehyde under thesame reaction conditions. No aldol adducts were obtained.



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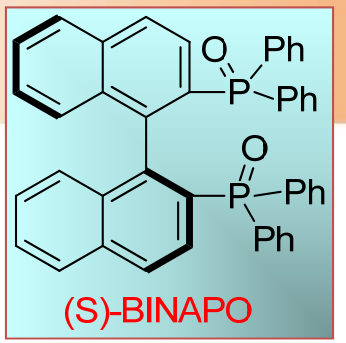
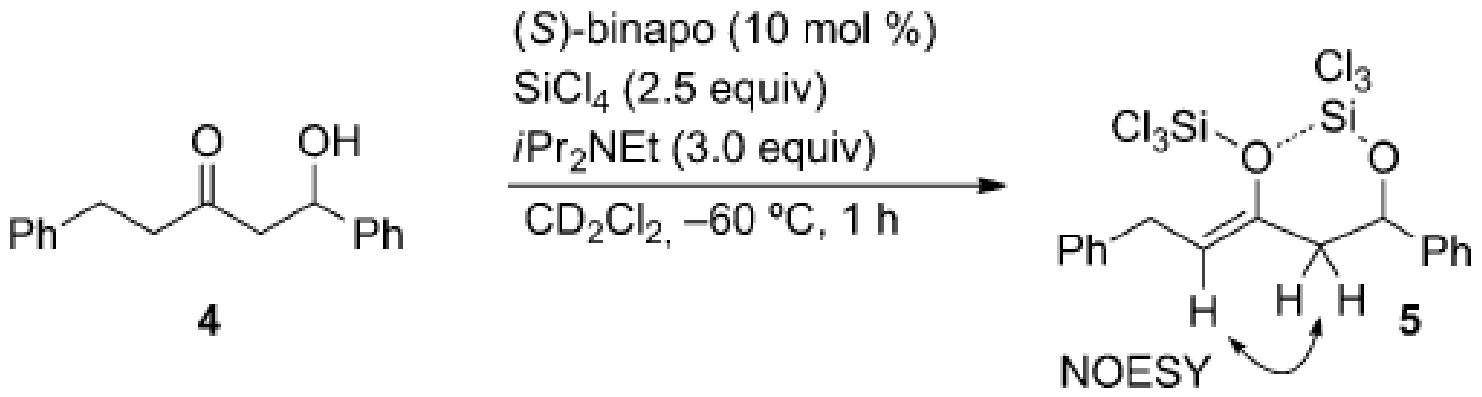


To investigate the second aldolization process, the author examined the NMR spectra associated with the enolization of the mono-aldol adduct 4. The1*H* NMR analysis showed the clean generation of the enol ether 5 as almost a single isomer, The NOESY correlation revealed that the geometry of 5 was the Z isomer.



Scheme 4. NMR experiment for the enolization of the aldol adduct 4.

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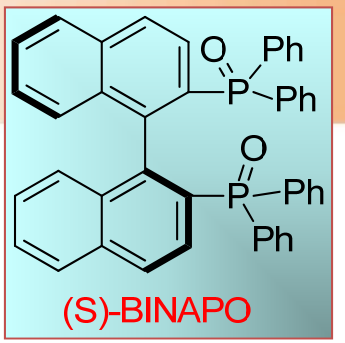
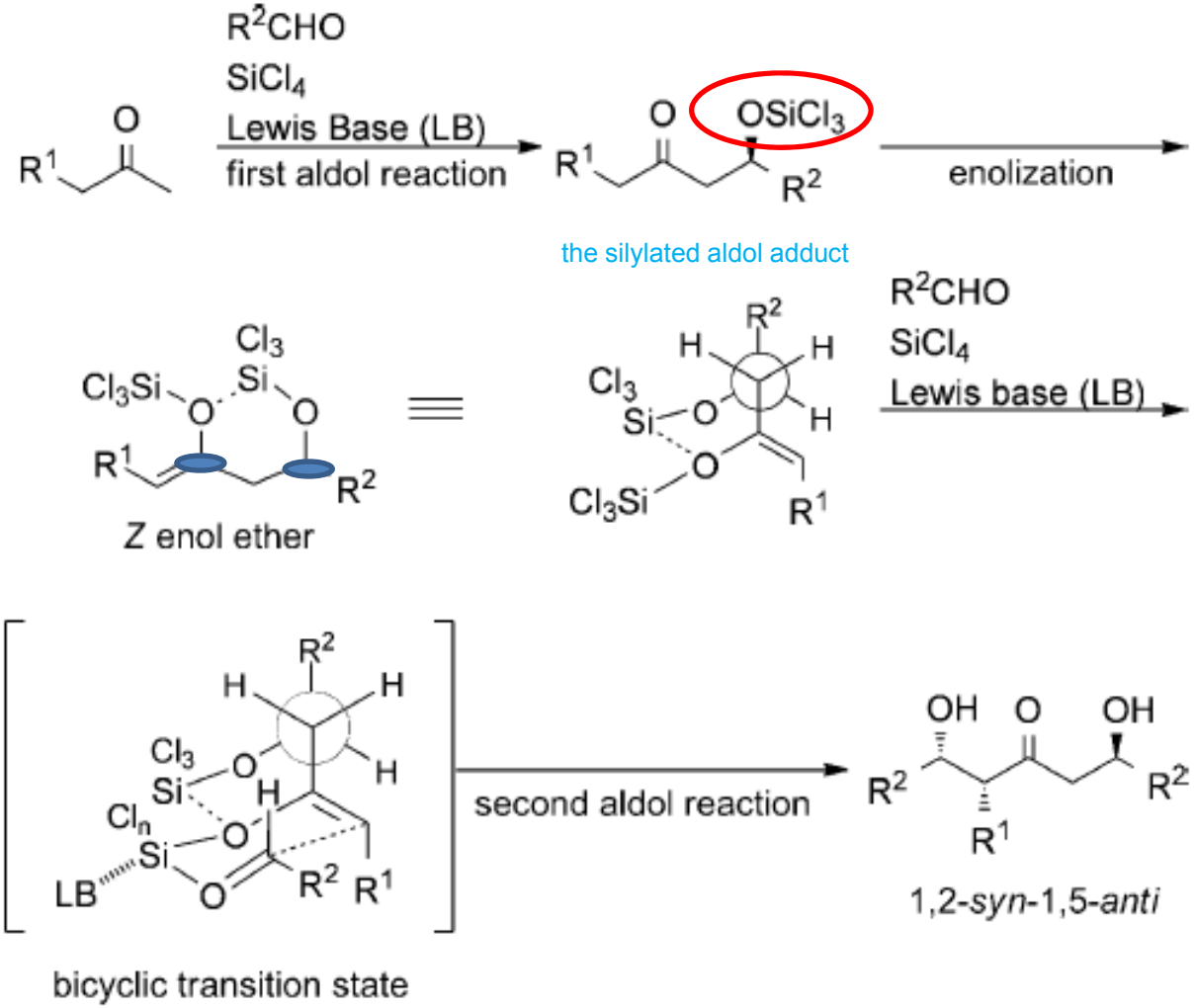
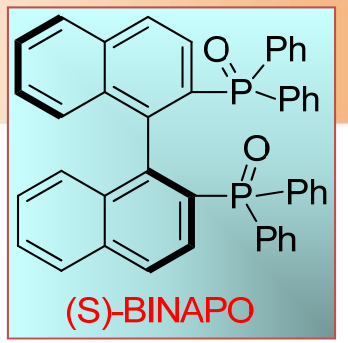




The second enolization step at the less congested exo position affords a chiral cyclic *Z*-silyl enol ether. The enol ether reacts with another aldehyde via a bicyclic six-membered transition state with the assistance of a Lewis base silicon complex, thus giving the 1,2-*syn*-1,5-*anti* product.

Scheme 5. Proposed reaction mechanism for the double aldol reaction.

Conclusion



a novel enantioselective double aldol reaction of an alkyl methyl ketone and two aldehydes using a chiral phosphine oxide as an organocatalyst.

The present reaction allows ready access to the 1,2-*syn*-1,5-*anti*-1,5-dihydroxy-3-pentanones with high stereoselectivity

in a single operation.

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Thanks !