N-silyl oxyketene imines are underused yet highly versatile reagents for catalytic asymmetric synthesis

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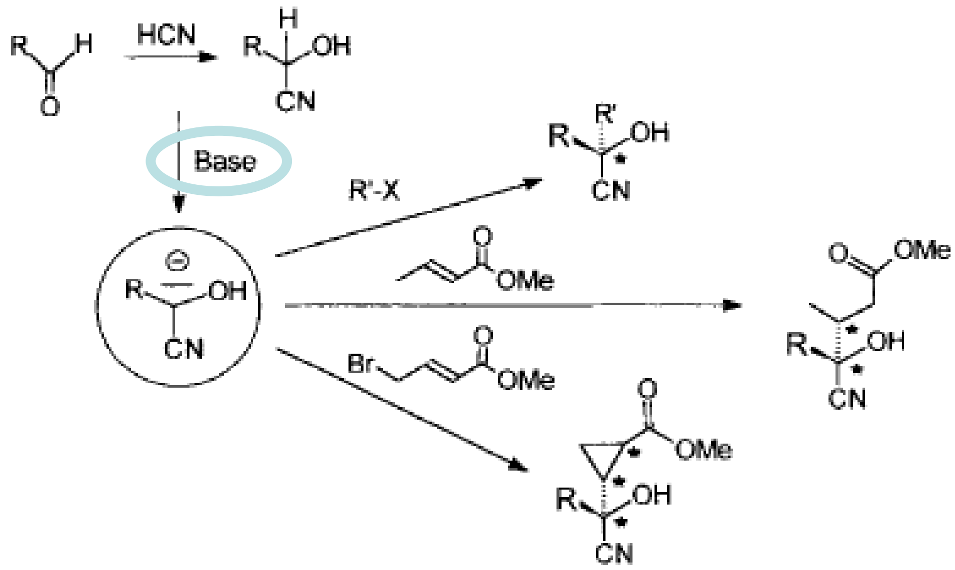
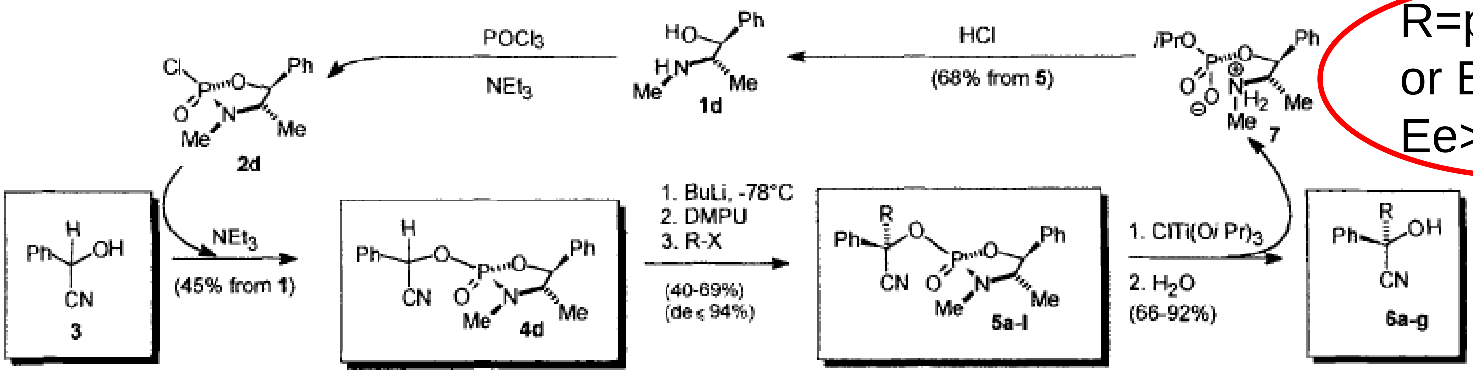
Metallo ketene imine from cyanohydrins



- Useful process for C-C bond construction
- Some limits in catalytic asymmetric synthesis

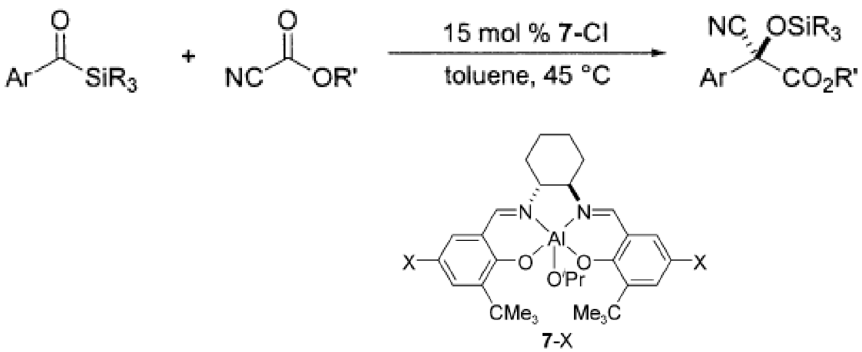
Use of metallo ketene imine in asymmetric syntheses



Scheme 3. Transformation of racemic aldehyde cyanohydrin **3** into optically active ketone cyanohydrins **6** with recycling of the ephedrine auxiliary **1**.

R=propargyl
or Bn
Ee>96%

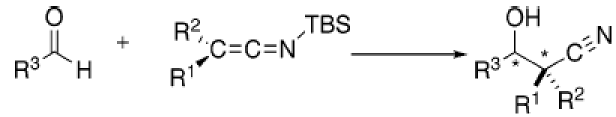
T. Schrader, *Chem*. *Eur. Joc* **1997**, 8, p. 1273

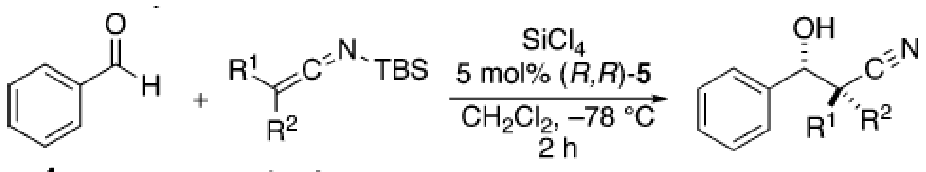


R=Et and R'=Ph
Ee=93%

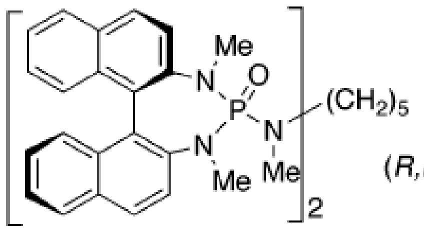
Nicewicz D.A,.Yates C. A, Jonhson J.S.
Angew. Chem. Int. Ed. **2004**, *43*, p. 2652

Use of N-silyl Ketene Imines in Asymmetric Aldol Reactions





4a 3a-d 6aa-6ad

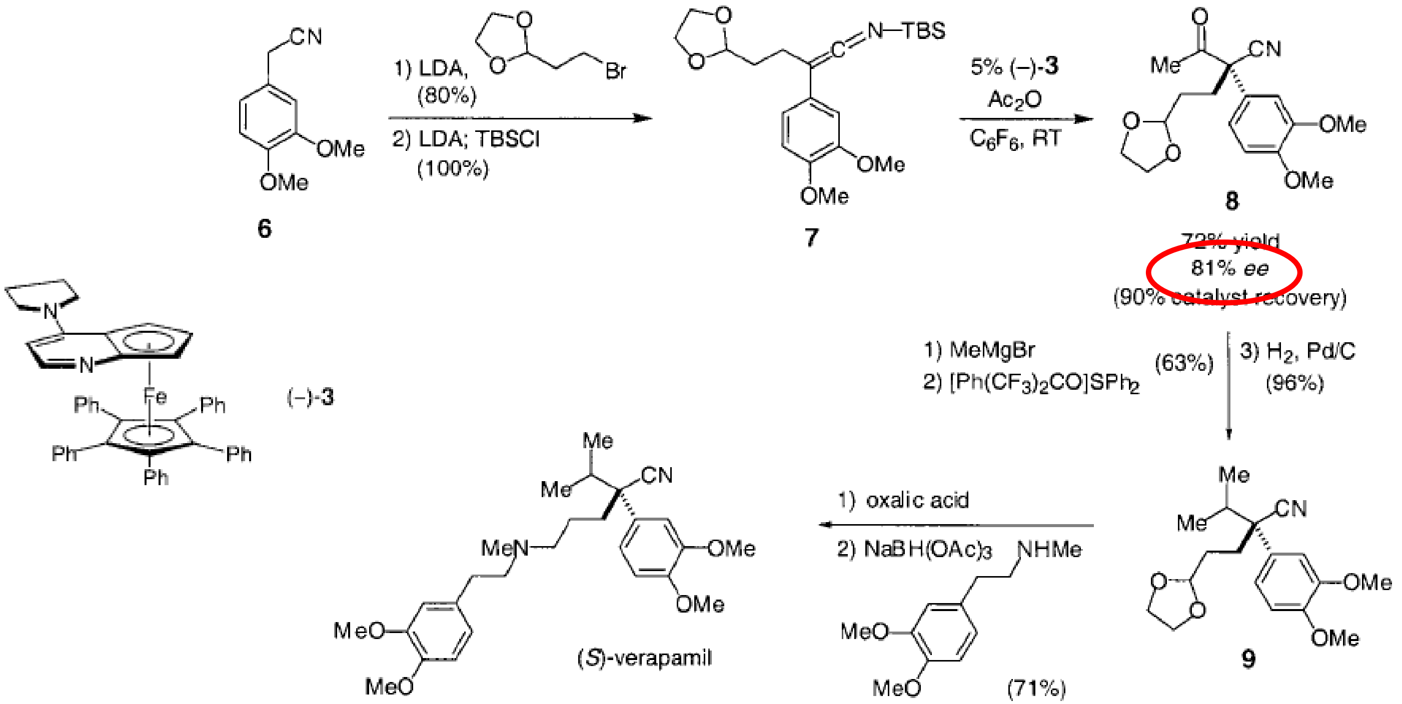


(*R*,*R*)-**5**

entry	SKI	R^1	R^2	product	yield %[b]	dr[c]	er[c]
1	**3a**	Ph	Me	**6aa**	87	95:5[d]	98.5:1.5
2	**3b**	4-$CF_3C_6H_4$	Et	**6ab**	73	97:3	99.5:0.5
3	**3c**	4-$MeOC_6H_4$	Me	**6ac**	90	99:1	99.1:0.9
4	**3d**	2-MeC_6H_4	Me	**6ad**	74	87:13[d]	94.2:5.8[e]

Denmark S. E, Wilson T. W, Burk, T, Heemstra J. R. *J. Am. Chem. Soc.* **2007**, *129*, p. 14864

Use of N-silyl Ketene Imines in Asymmetric Aldol Reactions

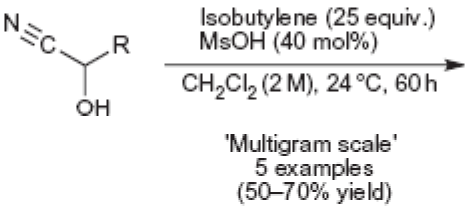


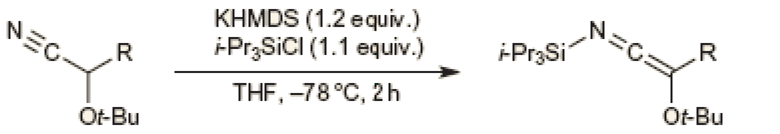
Scheme 2. Catalytic asymmetric synthesis of (S)-verapamil. LDA = lithium diisopropylamide.

Mermerian A. H, Fu G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, p. 949

Use of N-silyl Oxyketene Imines in Asymmetric Aldol Reactions

N-silyl oxyketene imine synthesis





3b–f **4b–f**

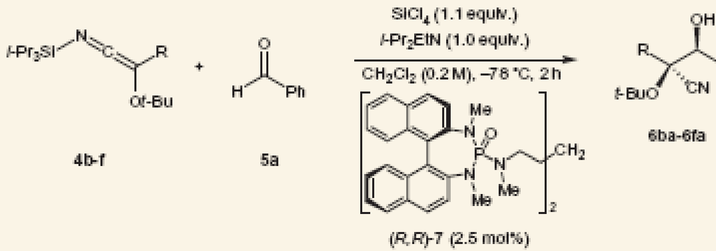
Entry	R	Product	Yield (%)*	υ_{max} (cm^{-1})†
1	Me	**4b**	94	2,037
2	Et	**4c**	94	2,033
3	*i*-Bu	**4d**	93	2,036
4	Bn	**4e**	93	2,039
5	Allyl‡	**4f**	97	2,037

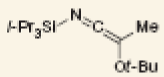
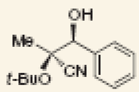
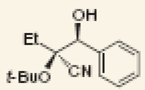
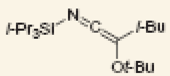
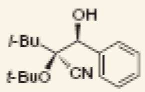
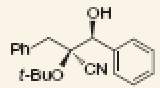
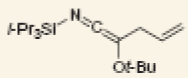
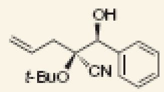
General reaction conditions: 3 (3.6–5.9 mmol), KHMDS (1.2 equiv.), *i*-Pr_3SiCl (1.1 equiv.), THF (1.0 M), −78 °C, 2 h. *Yield of crude ketene imine obtained after filtration and removal of volatiles by high vacuum. †FT-IR of neat liquids on NaCl plates. ‡Starting material prepared by alkylation of tert-butyl protected formaldehyde cyanohydrin.

Use of N-silyl Oxyketene Imines in Asymmetric Aldol Reactions

Aldol reaction of N-silyl oxyketene imines

Table 2 | Survey of *N*-silyl oxyketene imines in the addition to benzaldehyde catalysed by (*R*,*R*)-7.



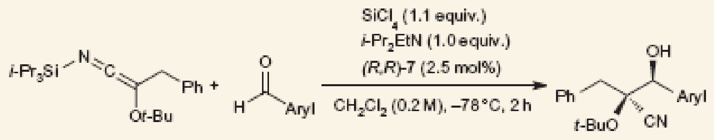
Entry	Nucleophile	Product	Yield (%)*	dr†	er‡
1	 4b	 6ba	84	96:4	>99:1§
2	 4c	 6ca	92	98:2	>99:1
3	 4d	 6da	92	98:2	>99:1
4	 4e	 6ea	93	99:1	>99:1
5	 4f	 6fa	90	99:1	>99:1

General reaction conditions: **5** (1.0 mmol), **4** (1.2 equiv.), (*R*,*R*)-**7** (2.5 mol%), $SiCl_4$ (1.1 equiv.), *i*-Pr_2EtN (1.0 equiv.), CH_2Cl_2 (0.2 M), −78 °C, 2 h. *Yield of analytically pure material. †Determined by ^1H NMR analysis of the crude reaction mixture. ‡Determined by chiral stationary phase supercritical fluid chromatography (CSP-SFC). §Determined by CSP-SFC analysis after conversion to the 3,5-dinitrobenzoyl ester.

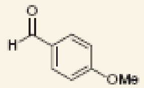
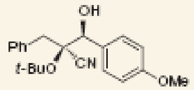
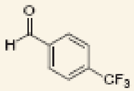
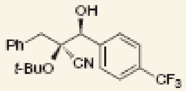
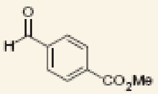
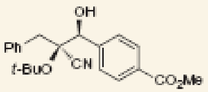
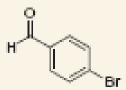
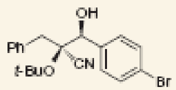
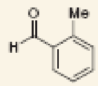
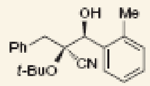
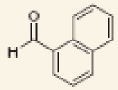
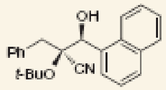
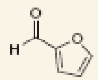
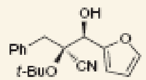
Use of N-silyl Oxyketene Imines in Asymmetric Aldol Reactions

Aldol reaction of N-silyl oxyketene imines

Table 3 | Survey of aromatic aldehydes in the addition of phenylacetaldehyde-derived ketene imine 4e.



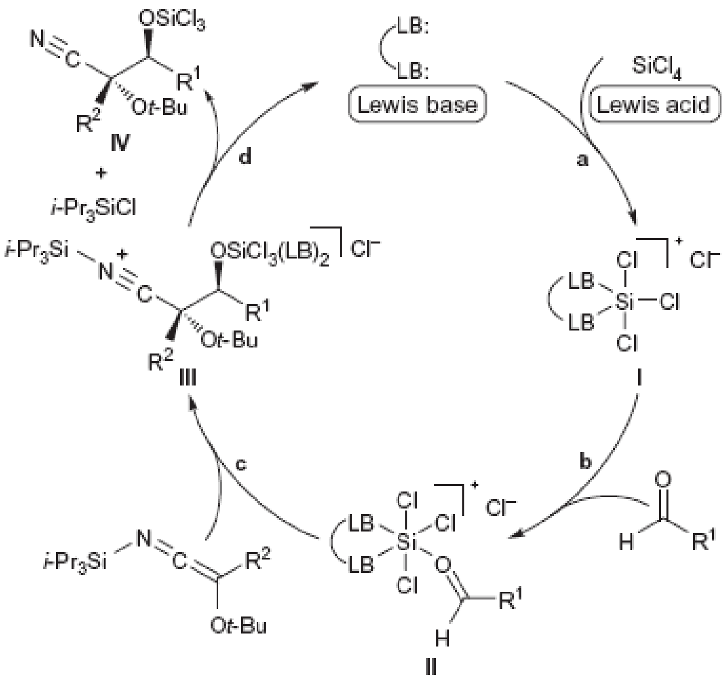
4e 5b–h 6eb–6eh

Entry	Aldehyde	Product	Yield (%)*	dr†	er‡
1	 5b	 6eb	93	98:2	>99:1
2	 5c	 6ec	93	99:1	>99:1
3	 5d	 6ed	91	98:2	98.6:1.4
4	 5e	 6ee	95	98:2	>99:1
5	 5f	 6ef	93	99:1	98.9:1.1
6	 5g	 6eg	89	99:1	93.5:6.5
7	 5h	 6eh	91	99:1	>99:1

General reaction conditions: 5 (1.0 mmol), 4 (1.2 equiv.), (*R*,*R*)-7 (2.5 mol%), $SiCl_4$ (1.1 equiv.), *i*-Pr_2EtN (1.0 equiv.), CH_2Cl_2 (0.2 M), −78 °C, 2 h. *Yield of analytically pure material. †Determined by ^1H NMR analysis of the crude reaction mixture. ‡Determined by CSP-SFC analysis.

Use of N-silyl Oxyketene Imines in Asymmetric Aldol Reactions

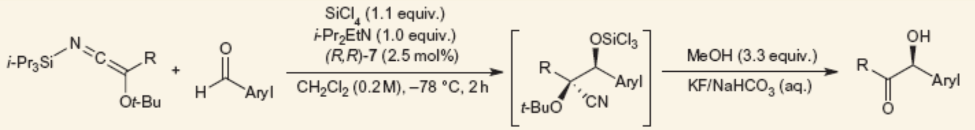
Aldol reaction of N-silyl oxyketene imines : plausible mechanism



Use of N-silyl Oxyketene Imines in Asymmetric Aldol Reactions

Transformation of the aldol product: cross benzoin reaction

Table 4 | Lewis base catalysed cross-benzoin reactions of *N*-silyl oxyketene imines with aromatic aldehydes.



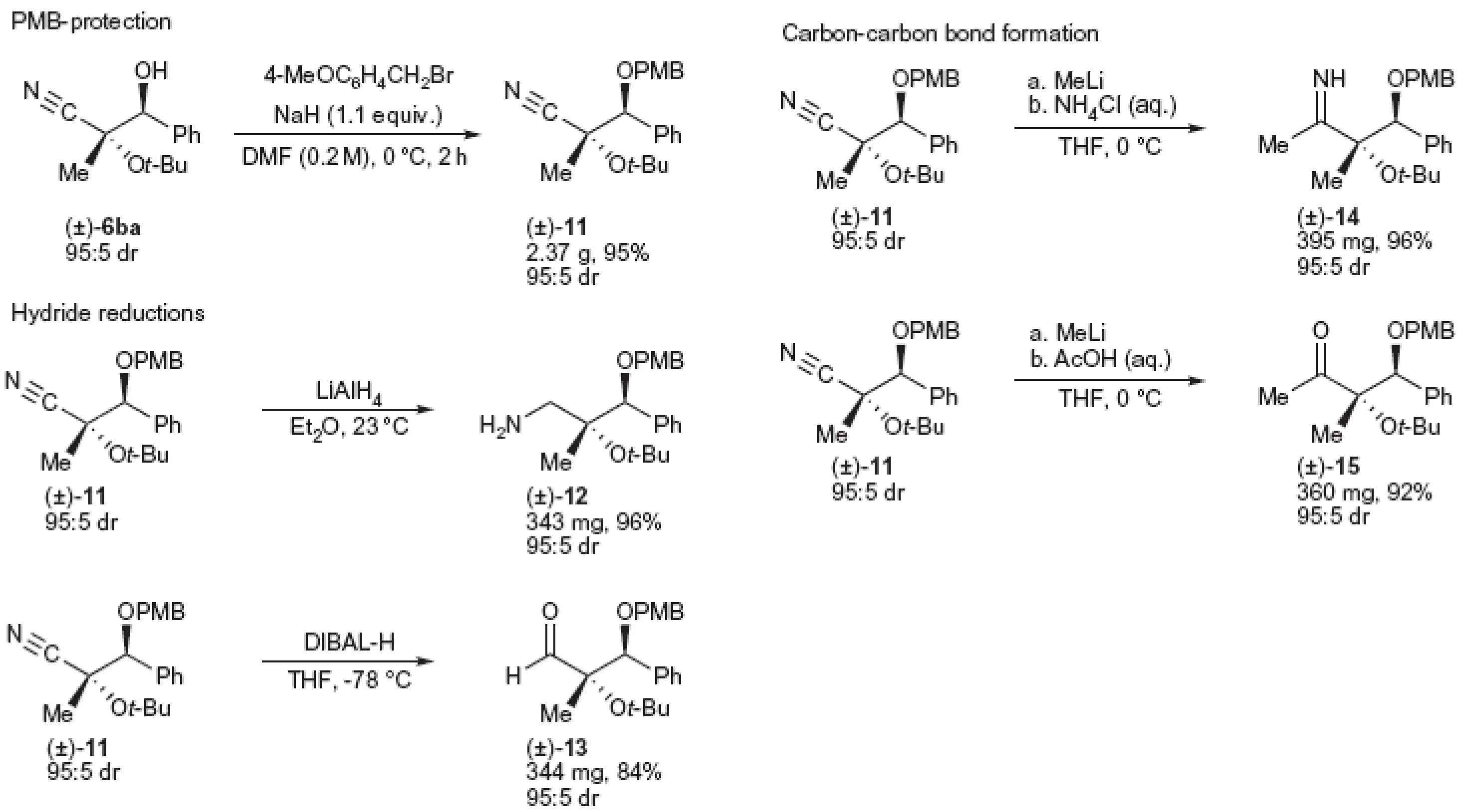
4c–e 5a–d 8 9ca–9ea & 9ea–ed

Entry	Nucleophile	Aldehyde	Product	Yield (%)	er
1	4c	5a	9ca	79*	99.0:1.0‡
2	4d	5a	9da	82*	98.9:1.1‡
3	4e	5a	9ea	84†	>99/1§
4	4e	5b	9eb	75†	>99/1§
5	4e	5c	9ec	77†	>99/1§,‖
6	4e	5d	9ed	78†	>99/1§,¶

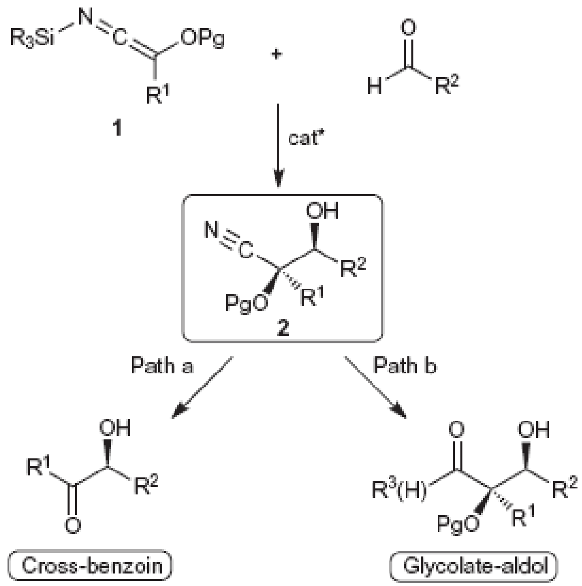
General reaction conditions: **5** (1.0 mmol), **4** (1.4 equiv.), (*R*,*R*)-**7** (2.5 mol%), $SiCl_4$ (1.1 equiv.), *i*-Pr_2EtN (0.2 equiv.), MeOH (3.3 equiv.), CH_2Cl_2 (0.2 M), −78 °C, 2 h. *Yield of chromatographically homogeneous material. †Yield of analytically pure material after single recrystallization from toluene. ‡Determined by CSP-SFC analysis on chromatographically homogeneous material. §Determined by CSP-SFC analysis after single recrystallization from toluene. ‖96.1:3.9 er was obtained before recrystallization. ¶96.5:3.5 er was obtained before recrystallization.

Use of N-silyl Oxyketene Imines in Asymmetric Aldol Reactions

Transformation of the aldol product:

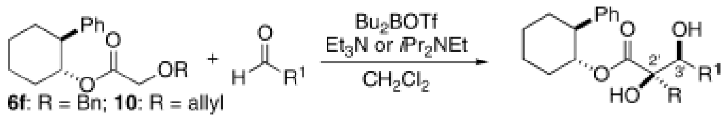


Conclusion



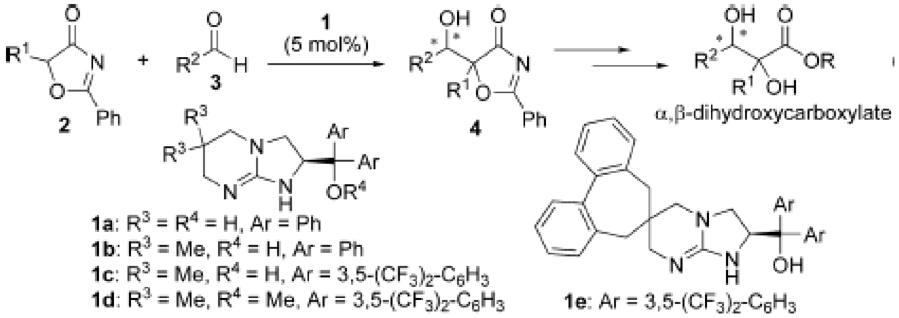
- Beta hydroxy cyanohydrins are obtained with exceptional dia and enantioselectivities
- Tetrasubstituted stereogenic centres are obtained
- Versatility

Asymmetric Aldol Reactions



Entry	R	R^1	Product	Yield[b]	(2'R,3'S):[c] (2'S,3'R)	ee after $LiAlH_4$ reduction[d]
1	Bn	Ph	**7f**	83%	20:1	89%
2	Bn	C_9H_{19}	**11**	88%	>20:1	95%
3	Bn	Cy	**12**	71%	20:1	91%
4	Bn	Ph	**13**	81%	>20:1	93%
5	Allyl	Ph	**14**	83%	20:1	90%
6	Allyl	C_9H_{19}	**15**	79%	8:1	75%
7	Allyl	*i*Pr	**16**	68%	20:1	89%
8	Allyl	Ph	**17**	59%	>20:1	95%

Giampietro. N.C, Kampf J. W, Wolfe J. P, *J. Am. Chem. Soc.* **2009**, *131*, p. 12556



Misaki T, Takimoto G, Sugimura T, *J. Am. Chem. Soc.* **2010** *132*, p. 6286

Syn/Anti : 98/2
Ee : Syn/anti : 96/26