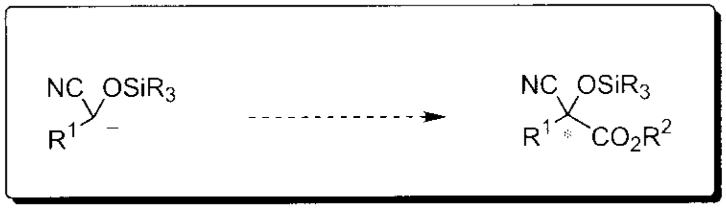
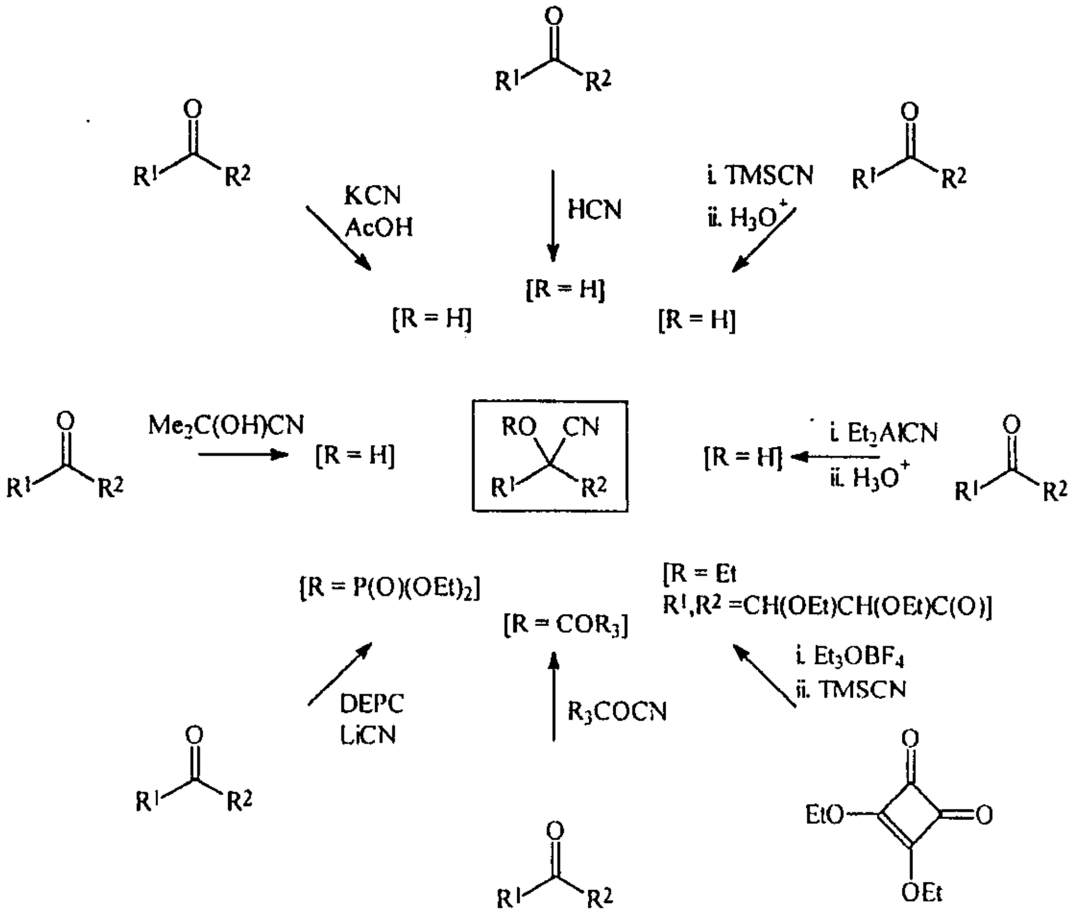
Catalytic Asymmetric Acylation of (Silyloxy)nitrile Anions

David A. Nicewicz, Christopher M. Yates, and Jeffrey S. Johnson

Angew. Chem. Int. Ed. **2002**, *43*, 2652-2655.

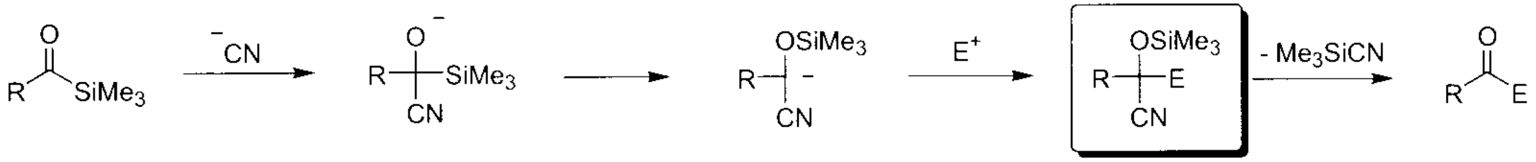


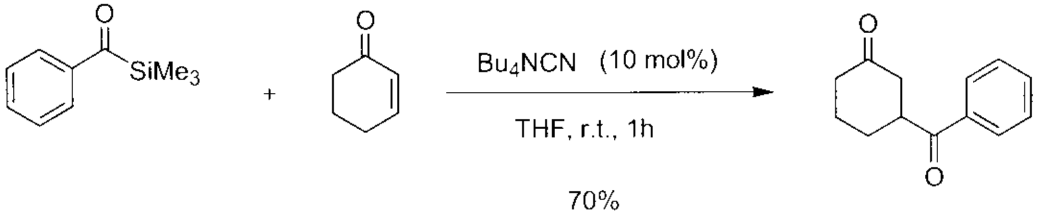
Some Common Methods for Hydrocyanation and Cyanation of Carbonyl Compounds

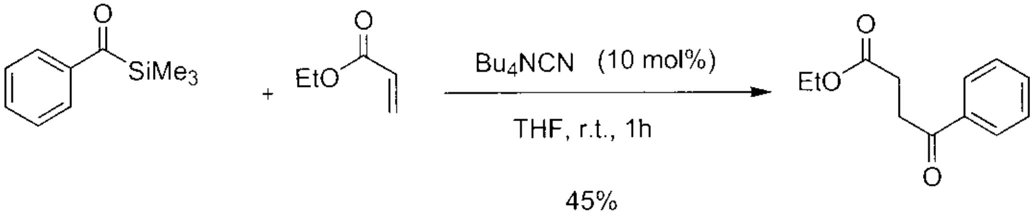


For a review on Cyanohydrins see: Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649.

Formation of Protected Cyanohydrins *via* Brook Rearrangement of Acylsilanes





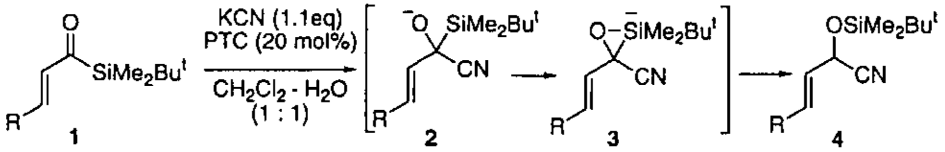


degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V.
Gazz. Chem. Ital. **1987**, *117*, 645.

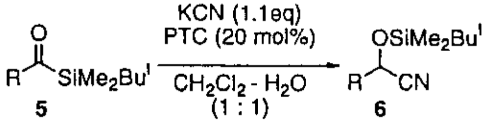
For a recent review on the Brook rearrangement: Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

Formation of Protected Cyanohydrins *via* Brook Rearrangement of Acylsilanes

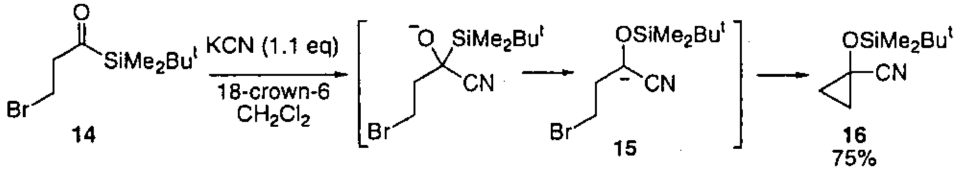
cyanohydrin isolation and interception of reactive intermediates



		yield (%)	
1	R	n-Bu$_4$NBr	n-Bu$_4$PBr
a	Me	75	82
b	i-Pr	56	93
c	c-C$_3$H$_5$	85	95
d	c-C$_6$H$_{11}$	64	96
e	t-Bu	85	95



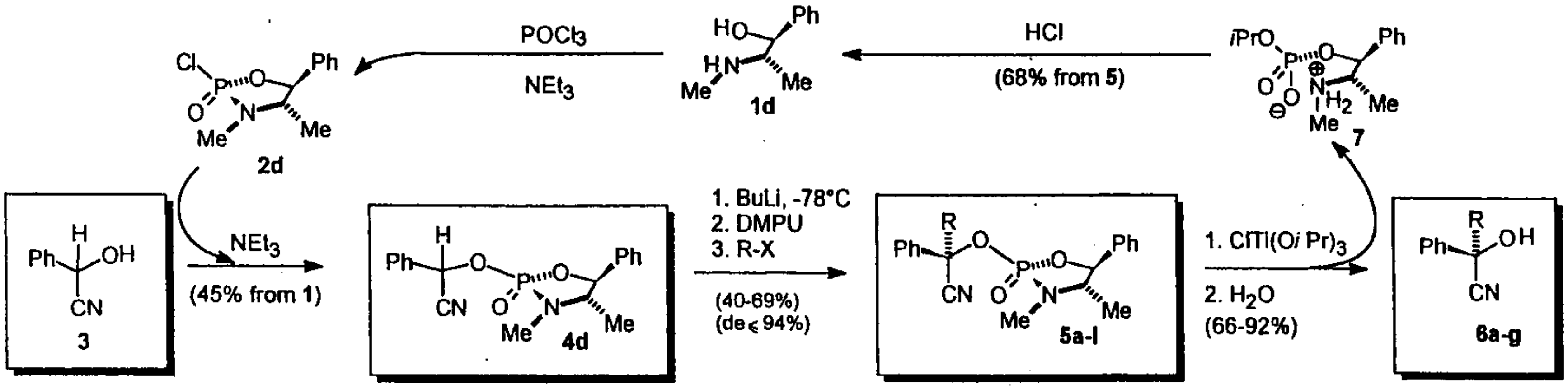
		yield (%)	
5	R	n-Bu$_4$NBr	n-Bu$_4$PBr
a	Ph	68	95
b	Me	65	74
c	CH$_2$CH$_2$OMe	65	76



Takeda, K.; Ohnishi, Y. *Tetrahedron Lett.* **2000**, *41*, 4169.

First Enantioselective Synthesis of Tertiary Cyanohydrins

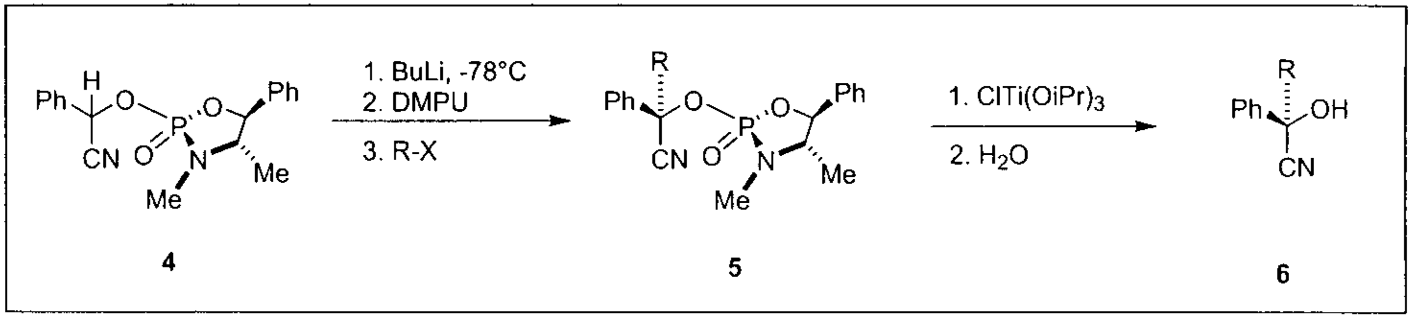
pseudoephedrine based chiral phosphate auxiliary



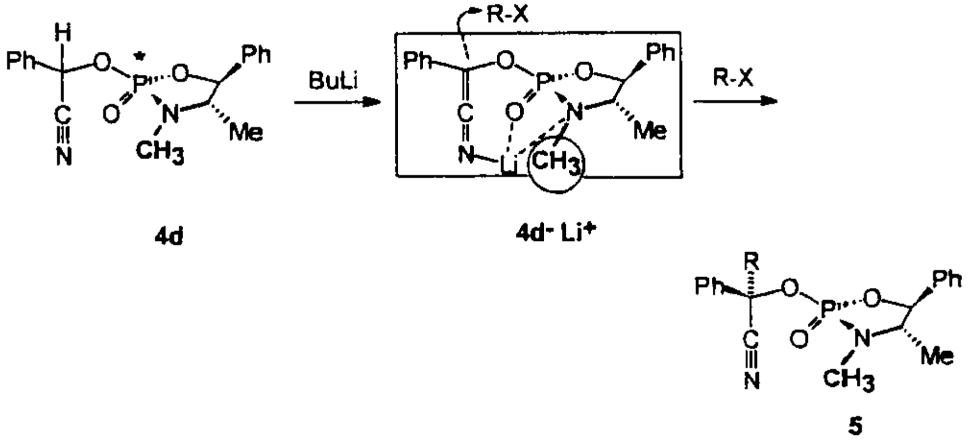
Scheme 3. Transformation of racemic aldehyde cyanohydrin **3** into optically active ketone cyanohydrins **6** with recycling of the ephedrine auxiliary **1**.

Schrader, T. *Chem. Eur. J.* **1997**, *3*, 1273.

First Enantioselective Synthesis of Tertiary Cyanohydrins

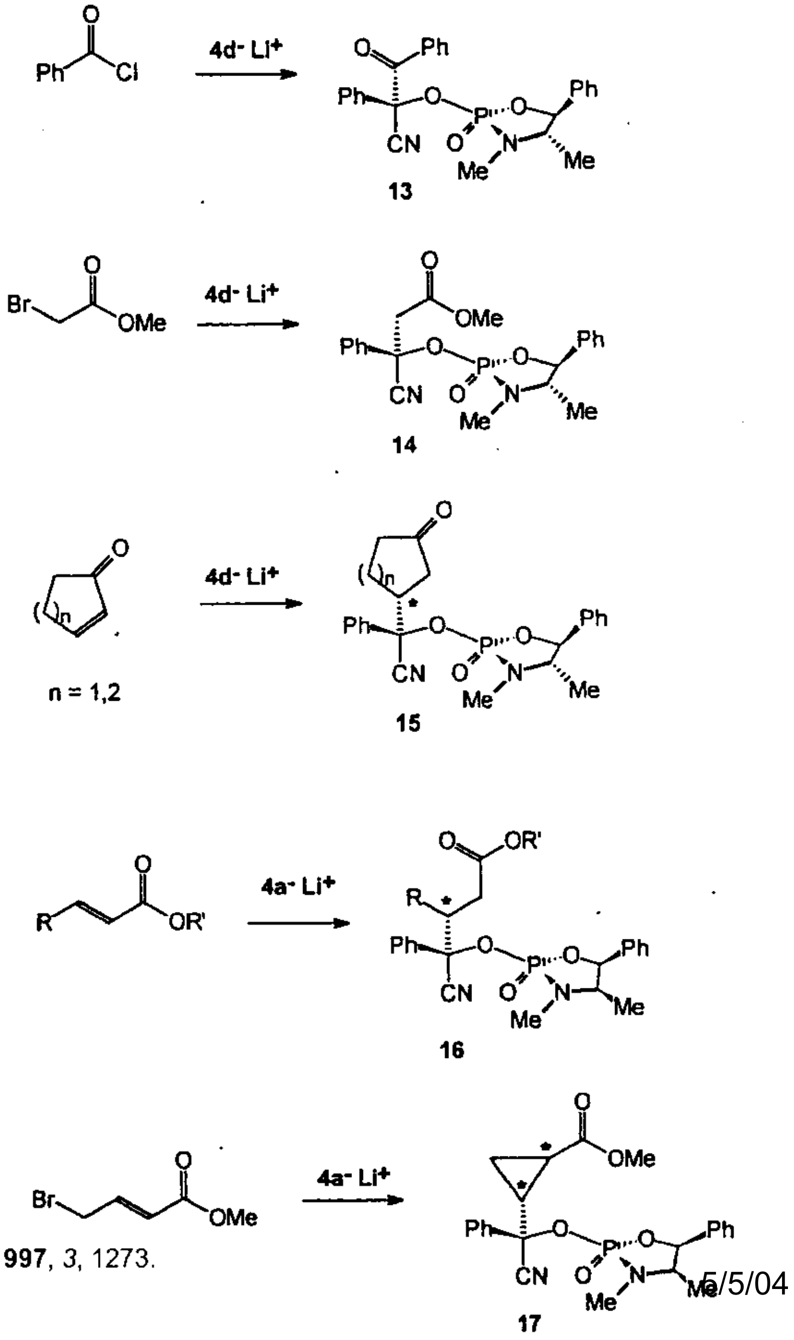


R	X	5	Yield (%)	*de* (%)	6	Yield (%)	*ee* (%) [a]
allyl	Br	a	47	90	a	79	
methyl	I	b	69	83	b	66	>96
n-propyl	I	c	58	82	c	92	
propargyl	Br	d	65	82	d	72	
benzyl	Br	e	58	82	e	85	>96
3-phenylpropyl	I	f	54	80	f	44	
(−)-myrtenyl	Br	g	49	48	g	58	
n-octyl	I	h	48	81			
3,3-dimethylallyl	Br	i	40	94			
2-bromoallyl	Br	k	38	71			
cinnamyl	Br	l	45	90			



Schrader, T. *Chem. Eur. J.* **1997**, *3*, 1273.

First Enantioselective Synthesis of Tertiary Cyanohydrins

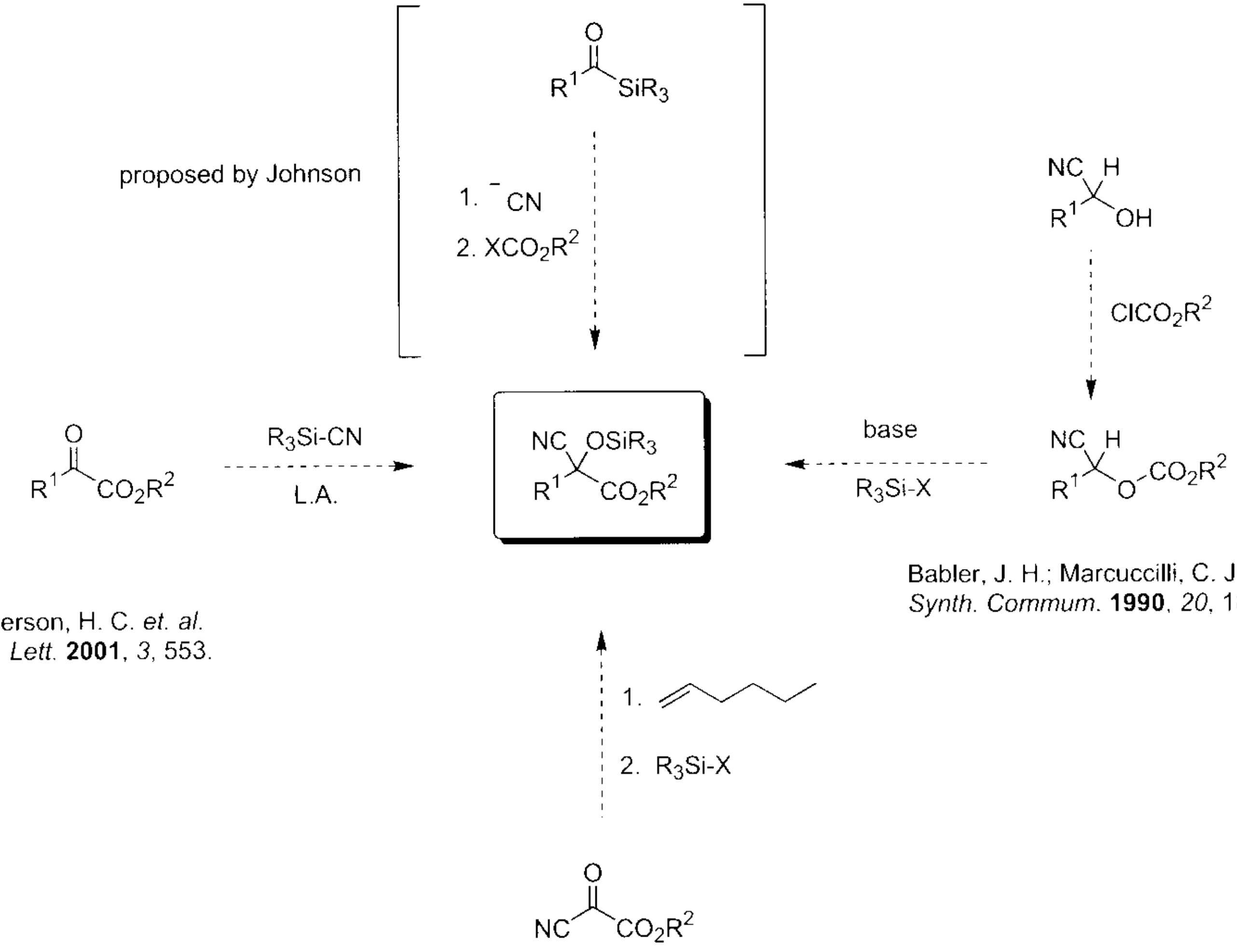


Electrophile	Product	Yield (%)	*dr* (%) [a]
benzoyl chloride	**13**	52	91:9
ethyl bromoacetate	**14**	53	83:17
2-cyclopentenone	**15a**	53	74:22:3: <1 [b]
2-cyclohexenone	**15b**	61	72:23:4: <1 [b]
ethyl crotonate	**16a**	55	80:13:5: <2 [b]
methyl cinnamate	**16b**	48	65:22:9: <4 [b]
methyl 4-bromocrotonate	**17**	69	55:27:12: <6 [c]

[a] *dr* = diastereomeric ratio. [b] Only three diastereomers could be detected; we assume an (*R*) configuration at C_γ for both major diastereomers. [c] No other diastereomers could be detected.

Schrader, T. *Chem. Eur. J.* **1997**, *3*, 1273.

Synthetic Approaches to α-Cyano-α-hydroxy Esters



Wilkerson, H. C. *et. al.*
Org. Lett. **2001**, *3*, 553.

Babler, J. H.; Marcuccilli, C. J.; Oblong, J. E.
Synth. Commum. **1990**, *20*, 1831.

Achmatowicz, O.; Szymoniak, J.
Tetrahedron **1982**, *38*, 1299.

Catalyzed Cyanation/Brook Rearrangement/C-Acylation Sequence

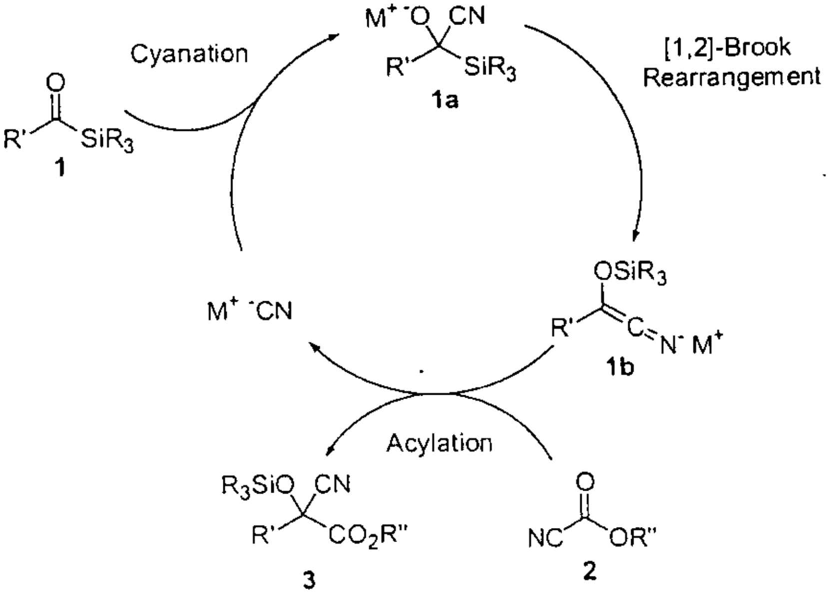
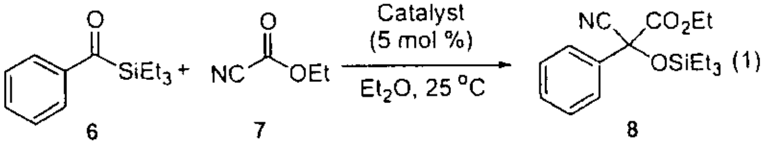


Table 1. Catalyst Evaluation for Cyanation/Brook Rearrangement/C-Acylation Reactions of Acylsilanes (Eq 1)[a]

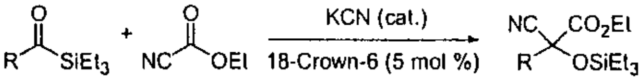


entry	catalyst	time (h)	yield (%)[b]
1	KCN	36	29[c]
2	KCN/18-crown-6	4–5	86
3	KCN/Bu_4NBr	15	83
4	KCN/Bu_4PBr	15	74
5	quinuclidine	36	69[d]
6	none	36	0

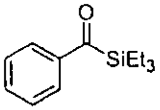
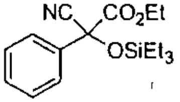
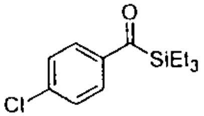
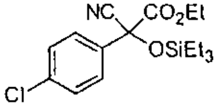
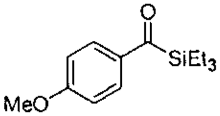
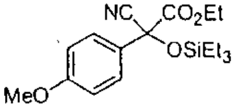
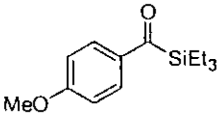
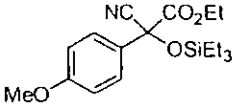
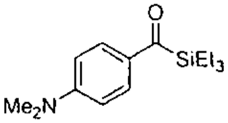
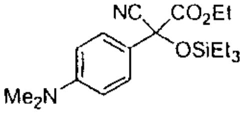
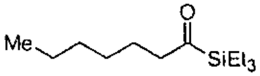
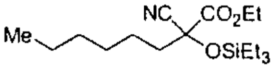
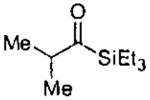
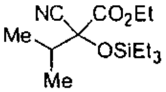
[a] PhC(O)$SiEt_3$ (1.0 equiv), $NCCO_2Et$ (1.1 equiv). [b] Isolated yield of analytically pure material. [c] Percent conversion based on ^1H NMR spectroscopy of the unpurified reaction mixture. [d] Catalyst concentration = 20 mol %, C_7H_8, 25 °C.

Linghu, X.; Nicewicz, D. A.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957.

Catalyzed Cyanation/Brook Rearrangement/C-Acylation Sequence



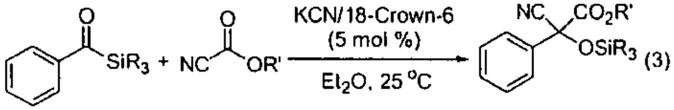
(2)

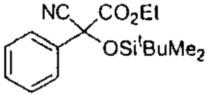
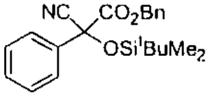
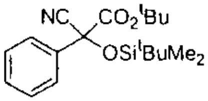
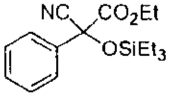
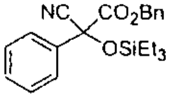
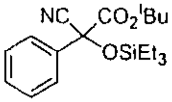
entry	acylsilane	product	solvent	temp (°C)	time (h)	yield[b] (%)
1			Et_2O	25	2	81
2			Et_2O	25	1	74
3			Et_2O	25	12	62[c]
4			C_7H_8	110	3	85[d]
5			C_7H_8	110	24	97
6			Et_2O	25	1.5	73[c]
7			Et_2O	25	1.5	61[c]

Linghu, X.; Nicewicz, D. A.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957.

Catalyzed Cyanation/Brook Rearrangement/C-Acylation Sequence

Table 3. Variation of Silane and Ester Substituents in Catalyzed Cyanation/Brook Rearrangement/C-Acylation Reactions (Eq 3)[a]



entry	acylsilane	(R')	product	time (h)	yield (%)[b]
1	$\mathrm{SiMe_2{}^tBu}$	Et		2	92
2	$\mathrm{SiMe_2{}^tBu}$	Bn		2	87
3	$\mathrm{SiMe_2{}^tBu}$	^{t}Bu		1	87
4	$\mathrm{SiEt_3}$	Et		2	81
5	$\mathrm{SiEt_3}$	Bn		2	80
6	$\mathrm{SiEt_3}$	^{t}Bu		12	72

[a] $\mathrm{PhC(O)SiR_3}$ (1.0 equiv), $\mathrm{NCCO_2R'}$ (1.1 equiv). [b] Isolated yield of analytically pure material; average of at least two experiments.

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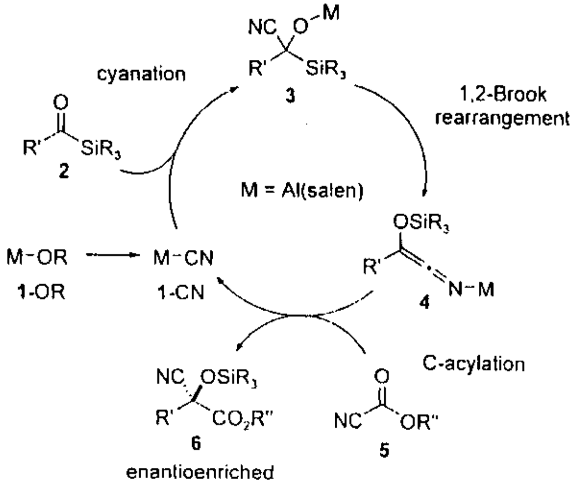

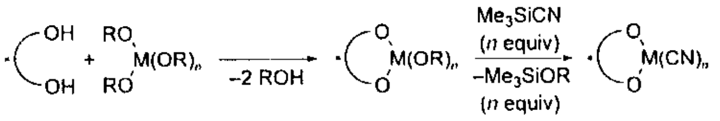

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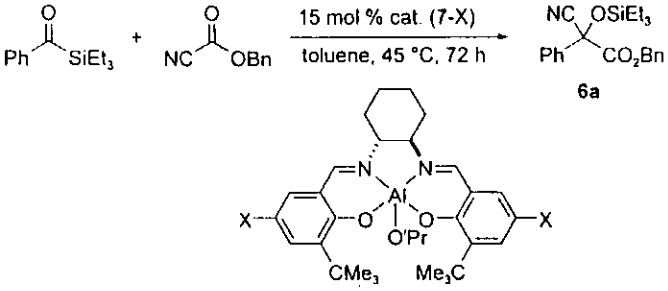


(2)

7-X

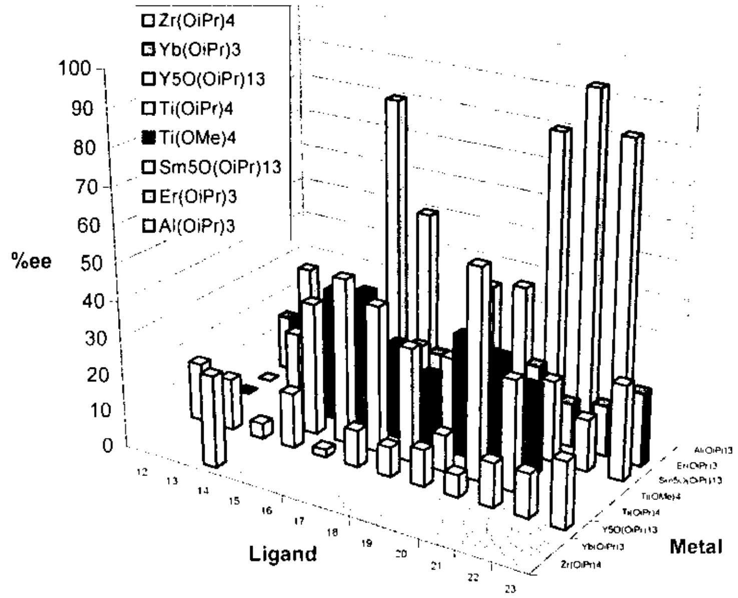
Table 1: Optimization of catalyzed reactions of acylsilanes and cyanoformate esters [Eq. (2)].[a]

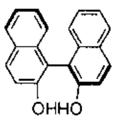
Entry	X in 7-X	c_0(PhC(O)SiEt$_3$) [M]	*ee*[b] [%]	Conv. [%][c]
1	CMe$_3$	2.5	26	> 95
2	CMe$_3$	1.5	34	> 95
3	CMe$_3$	0.5	46	80
4	NO$_2$	2.5	44	> 95
5	NO$_2$	1.5	54	90
6	NO$_2$	0.5	54	30
7	Cl	2.5	56	> 95
8	Cl	1.5	62	> 95
9	Cl	0.5	67	> 95
10	Cl	0.05	79	> 95
11	OMe	0.05	70	> 95
12	NMe$_2$	0.05	46	> 95

[a] PhC(O)SiEt$_3$ (1.0 equiv), BnO$_2$CCN (2.0 equiv). [b] Determined by CSP-SFC. [c] Determined by ^{1}H NMR spectroscopy.

Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 2652.

Catalytic Asymmetric Acylation of (Silyloxy)nitrile Anions





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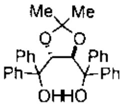

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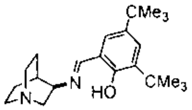

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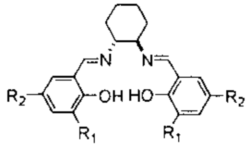
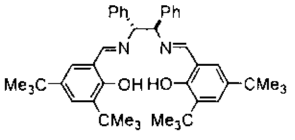
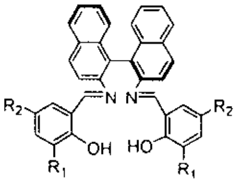


15 $R_1 = R_2 = CMe_3$
16 $R_1 = R_2 = H$
17 $R_1 = Me$; $R_2 = H$
18 $R_1 = OMe$; $R_2 = H$
19 $R_1 = H$; $R_2 = Cl$
20 $R_1 = R_2 = CMe_3$;
$R_1' = R_2' = H$



21

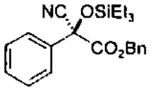
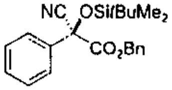
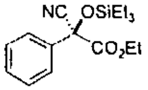
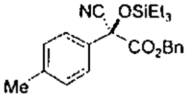
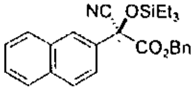
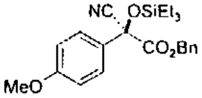
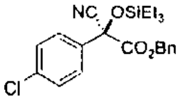
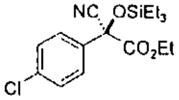
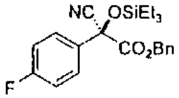
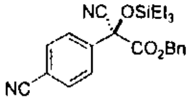


22 $R_1=R_2=H$
23 $R_1=R_2=CMe_3$

Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 2652.

Catalytic Asymmetric Acylation of (Silyloxy)nitrile Anions

Table 2: Catalytic asymmetric cyanation/Brook rearrangement/C-acylation of acylsilanes [Eq. (3)].[a]

Entry	Ar	SiR_3	R'	Product		Yield [%][b]	*ee* [%][c]
1	Ph	$SiEt_3$	Bn		6a	83	79[d]
2	Ph	$SitBuMe_2$	Bn		6b	82[e]	64[d]
3	Ph	$SiEt_3$	Et		6c	93[f]	77[d,g]
4	$4\text{-}MeC_6H_4$	$SiEt_3$	Bn		6d	79	80[h]
5	2-naphthyl	$SiEt_3$	Bn		6e	90	62[h]
6	$4\text{-}MeOC_6H_4$	$SiEt_3$	Bn		6f	84[i]	82[h]
7	$4\text{-}ClC_6H_4$	$SiEt_3$	Bn		6g	87	64[h,i]
8	$4\text{-}ClC_6H_4$	$SiEt_3$	Et		6h	87	61[d,g]
9	$4\text{-}FC_6H_4$	$SiEt_3$	Bn		6i	81	78[h,i]
10	$4\text{-}NCC_6H_4$	$SiEt_3$	Bn		6j	70	64[h]

Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 2652.

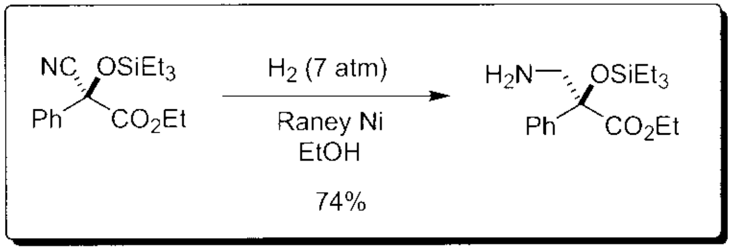
Summary

- Cyanohydrins are valued in organic synthesis for their umpolung reactivity.

- They also have vast potential as chiral building blocks so access to enantiopure substrates is desirable.

- The first catalytic asymmetric reaction of protected cyanohydrins has been developed.

- This domino sequence of cyanation/Brook rearrangement/C-acylation may serve as an efficient synthetic route for accessing enantioenriched and protected β-amino-α-hydroxy-α-aryl acids following reduction.



- Future work will focus on trapping the chiral (silyloxy)nitrile anions in other stereoselective bond forming reactions.