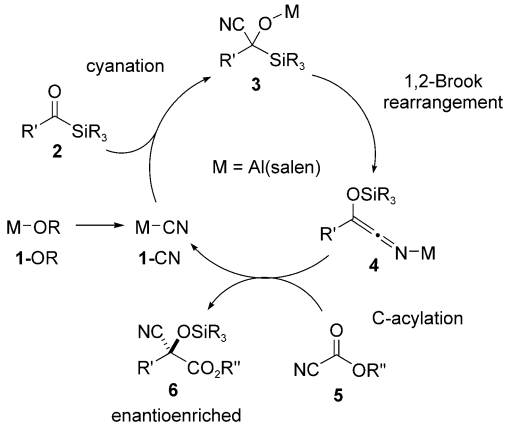
Cyanohydrin Anions

Catalytic Asymmetric Acylation of (Silyloxy)nitrile Anions**

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

Anions of protected cyanohydrins are useful intermediates in the formation of carbon–carbon bonds.[1–4] These stabilized carbanions offer considerable potential for asymmetric synthesis, but stereoselective transformations involving them are surprisingly rare.[5–8] One barrier to enantioselective catalysis is the apparent requirement of one equivalent of a strong base to generate the key carbanionic species. As an alternative, we considered the possibility that protected cyanohydrin anions might be generated by the reaction of chiral metal cyanide complexes with acylsilanes. This hypothesis was predicated on the observation of the facile Brook rearrangement of acylsilanes in the presence of alkali metal cyanides.[9–12] Here we describe the successful development of asymmetric cyanation/1,2-Brook rearrangement/C-acylation reactions of acylsilanes mediated by (salen)aluminum alkoxides (Scheme 1). These represent, to the best of our knowledge,



Scheme 1. Catalytic asymmetric acylation of (silyloxy)nitrile anions.

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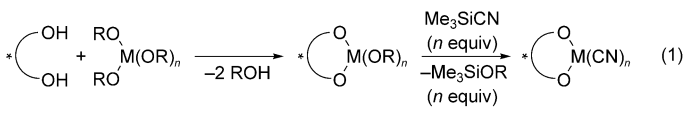
the first catalytic asymmetric reactions of protected cyanohydrin anions.

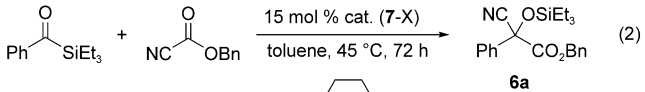
In an attempt to render the acylation of (silyloxy)nitrile anions[13] enantioselective, we chose to investigate a variety of chiral metal cyanide sources. We speculated that such complexes might be conveniently prepared according to Equation (1). Ligand exchange between a chiral diol and a



(1)

metal alkoxide should result in loss of two equivalents of alcohol and formation of a new, chiral metal alkoxide. Upon treatment with the appropriate amount of Me_3SiCN, chiral metal cyanide complexes were expected.

Evaluation of 96 metal–ligand complexes prepared by the described protocol revealed the Jacobsen (salen)aluminum complexes[14] as promising candidates for effecting the catalyzed acylation with good enantiocontrol [Eq. (2)].[15]



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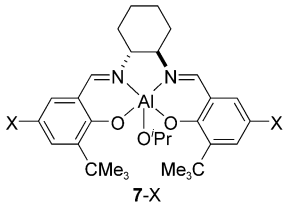


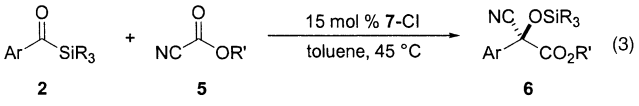
Optimization experiments, the results of which are summarized in Table 1, demonstrated that: 1) The reaction may be conducted with the metal alkoxide in the absence of Me_3SiCN as activator; the observation of the mixed carbonate *i*PrOC(O)OBn by ^{1}H NMR spectroscopy suggests that the metal alkoxide reacts with benzyl cyanoformate[16] to form a catalytically active (cyanido)aluminum complex (**1**-OR → **1**-CN, Scheme 1). 2) The enantioselectivity is subject to significant effects of remote substituents on the ligand, with a *para*-chlorine substituent delivering optimal results (79% *ee*, entry 10). 3) The enantioselectivity is strongly dependent on concentration: in dilute solutions, more highly enantioenriched acylated products are formed.

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_2CCN (2.0 equiv). [b] Determined by CSP-SFC. [c] Determined by ^{1}H NMR spectroscopy.

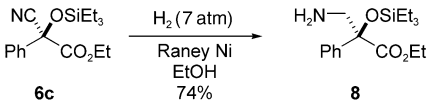
With good levels of enantiocontrol achieved using complex **7**-Cl, we investigated the scope of the reaction. Acylsilanes bearing a variety of aryl substituents (Ar) with either triethylsilyl or *tert*-butyldimethylsilyl groups (SiR_3) were treated with either benzyl or ethyl (R′) cyanoformate in the presence of catalytic amounts of **7**-Cl to give the desired enantioenriched cyano ester products **6** [Eq. (3)]. The results



(3)

of these experiments are summarized in Table 2. Varying the silyl group led to a significant reduction in selectivity (entries 1 and 2). Conversely, variation of the cyanoformate made little or no difference on either yield or enantioselectivity (see entries 1 vs. 3 and 7 vs. 8). Electron-donating substituents on the aryl ring of the acylsilane (entries 4 and 6) provided good levels of enantioinduction (up to 82% *ee*, entry 6), while the enantioenrichment with their electron-withdrawing counterparts (entries 5, 7, 8, and 10) was only moderate (61–64% *ee*). The only exception was 4-$FC_6H_4C(O)SiEt_3$ (78% *ee*, entry 9). Overall, the substrates examined gave moderate to good enantioselectivities with good to excellent yields. An air-stable aluminum oxo complex derived from the *p*-Cl-salen ligand, [(Cl-salen)Al(O)Al(salen-Cl)],[14c] effected the formation of **6a** with identical selectivity (80% *ee*) as complex **7**-Cl (entry 1). Alkyl acylsilanes (MeC(O)SiMe$_3$, *i*PrC(O)SiEt$_3$) were unreactive under (salen)Al catalysis, in contrast to catalysis by KCN/[18]crown-6.[13]

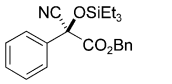
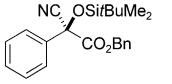
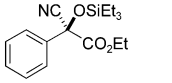
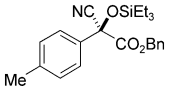
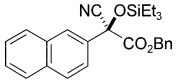
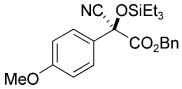
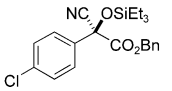
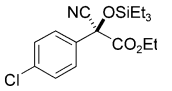
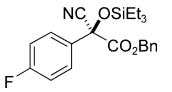
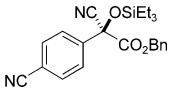
The products of the asymmetric cyanation/Brook rearrangement/C-acylation sequence are fully substituted malonic acid derivatives. Preliminary experiments suggest that the dense functionality may be selectively manipulated: exposure of adduct **6c** to Raney Ni/H_2 results in reduction of the nitrile group to afford the protected β-amino-α-hydroxy-α-phenyl acid derivative **8** in 74% yield [Eq. (4)].



(4)

In summary, a new catalytic asymmetric cyanation/1,2-Brook rearrangement/C-acylation reaction of acylsilanes with cyanoformates was developed. Access to chiral (silyloxy)nitrile anions is facilitated by metal cyanide-promoted Brook rearrangement reactions of acylsilanes. The asymmetric acylsilane/cyanoformate coupling provides compounds (**6**)

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	$SiEt_2tBuMe$	Bn		**6b**	82[e]	64[d]
3	Ph	$SiEt_3$	Et		**6c**	93[f]	77[d,g]
4	4-MeC_6H_4	$SiEt_3$	Bn		**6d**	79	80[h]
5	2-naphthyl	$SiEt_3$	Bn		**6e**	90	62[h]
6	4-$MeOC_6H_4$	$SiEt_3$	Bn		**6f**	84[i]	82[h]
7	4-ClC_6H_4	$SiEt_3$	Bn		**6g**	87	64[h,j]
8	4-ClC_6H_4	$SiEt_3$	Et		**6h**	87	61[d,g]
9	4-FC_6H_4	$SiEt_3$	Bn		**6i**	81	78[h,j]
10	4-NCC_6H_4	$SiEt_3$	Bn		**6j**	70	64[h]

[a] $ArC(O)SiR_3$ (1.0 equiv, 0.05 M), $NCCO_2R'$ (2.0 equiv) for 72 h unless otherwise noted. [b] Yield of analytically pure material; average of at least two experiments. [c] Determined by CSP-SFC analysis of the adduct, unless otherwise noted. [d] Absolute configuration determined by correlation to a compound of known configuration. See the Supporting Information for details. [e] 20 mol% catalyst used. [f] $c_0(\mathbf{2}) = 0.025$ M. [g] Determined by CSP-SFC analysis after reduction of the nitrile and coupling to (*S*)-mandelic acid. See Supporting Information for details. [h] Absolute configuration assigned by analogy. [i] $c_0(\mathbf{2}) = 0.1$ M. [j] Determined by CSP-SFC analysis after reduction of the nitrile and protection as the *N*-Boc carbamate. See the Supporting Information for details.

that may be considered formally as products of $R_3Si{-}CN$ addition to α-keto esters, a transformation that has yet to be rendered asymmetric. The interception of intermediates like **4** (Scheme 1) in other stereoselective bond constructions will be the focus of future work.

Experimental Section

Synthesis of **6a** (representative procedure): A flame-dried Schlenk tube equipped with a magnetic stir bar was charged with the aluminum complex **7**-Cl (19.4 mg, 0.033 mmol, 0.15 equiv) under Ar. Acylsilane (60 mg, 0.27 mmol, 1.0 equiv), benzyl cyanoformate (88 mg, 0.54 mmol, 2.0 equiv), and toluene (5.4 mL, 0.05 M) were all added to the Schlenk tube under Ar, and the tube was sealed and heated to 45 °C. After 72 h the flask was cooled to 25 °C, the solvent was removed under vacuum, and the crude product was purified by flash chromatography with 95:5 petroleum ether/EtOAc to afford 85.3 mg (83%) of **6a** as a colorless oil in 79% *ee* as determined by CSP-SFC analysis (CSP = chiral stationary phase, SFC = supercritical fluid chromatography; Chiralpak OD, 0.3% MeOH, 0.5 mL min^{-1}, 10 atm, 40 °C, 240 nm, $t_{R(major)} = 37.0$, $t_{R(minor)} = 41.5$ min). Analytical data for **6a**: $[\alpha]_D^{25} = +4.2$ ($c = 1.97$, CH_2Cl_2); IR (thin film): $\tilde{\nu} = 3067$, 3035, 2958, 2878, 2245, 1766, 1588, 1451, 1241, 1152, 1003, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.63$–7.61 (m, 2H), 7.38–7.35 (m, 3H), 7.29–7.26 (m, 3H), 7.19–7.17 (m, 2H), 5.17 (s, 2H), 0.93 (t, $J = 7.6$ Hz, 9H), 0.70 ppm (q, $J = 7.6$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.1$, 134.5, 129.9, 128.9, 128.8, 128.7, 128.2, 125.7, 118.3, 75.1, 68.9, 6.8, 5.4 ppm; TLC (95:5 hexanes/EtOAc): $R_f = 0.35$; elemental analysis calcd for $C_{22}H_{27}NO_3Si$: C 69.25, H 7.13, N 3.67; found: C 69.37, H 7.28, N 3.60.

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