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Mechanism and Scope of the Cyanide-Catalyzed Cross Silyl Benzoin Reaction

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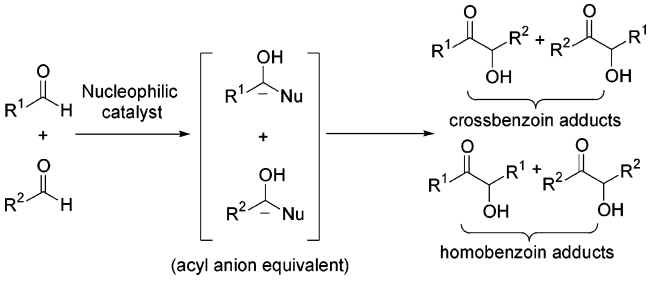
Abstract: In this work, cross silyl benzoin addition reactions between acylsilanes (**1**) and aldehydes (**2**) catalyzed by metal cyanides are described. Unsymmetrical aryl-, heteroaryl-, and alkyl-substituted benzoin adducts can be generated in moderate to excellent yields with complete regiocontrol using potassium cyanide and a phase transfer catalyst. From a screen of transition metal cyanide complexes, lanthanum tricyanide was identified as an improved second-generation catalyst for the cross silyl benzoin reaction. A study of the influence of water on the KCN-catalyzed cross silyl benzoin addition revealed more practical reaction conditions using unpurified solvent under ambient conditions. A sequential silyl benzoin addition/cyanation/O-acylation reaction that resulted in two new C−C bonds was achieved in excellent yield. The mechanism of cross silyl benzoin addition is proposed in detail and is supported by crossover studies and a number of unambiguous experiments designed to ascertain the reversibility of key steps. No productive chemistry arises from cyanation of the more electrophilic aldehyde component. Formation of the carbon−carbon bond is shown to be the last irreversible step in the reaction.

Introduction

The α-hydroxycarbonyl group is an important synthon for the synthesis of natural products, chiral auxiliaries, and ligands.[1] Among numerous synthetic strategies for introducing this moiety, the benzoin condensation and related additions[2−10] remain perhaps the most direct. In traditional metal cyanide-catalyzed benzoin condensations, both aromatic and heteroaromatic aldehydes can be transformed into α-hydroxy ketones. The substrate scope of the classic benzoin condensation was extended to enolizable aliphatic aldehydes by employing thiazolium carbenes as catalysts.[4,5] The mechanism of the benzoin condensation has been extensively studied by many groups; definitive contributions in the study of the cyanide system came from Lapworth[11] and Schowen,[12] and from Breslow[13,14] and Leeper[15] for thiazolium carbene catalysis.

Scheme 1



Since all of the steps in the benzoin condensation are typically reversible, its principal limitation arises in the coupling of two different aldehydes; the product distribution of the cross benzoin condensation is generally thought to be determined by the relative thermodynamic stability of the four possible products (Scheme 1). In some cases, regioisomeric mixtures can be avoided if one of the two aldehydes is employed in excess.[7c] To obtain the contrathermodynamic regioisomer, stoichiometric carbonyl umpolung reagents, such as dithianes[16,17] and protected cyanohydrin derivatives,[18,19] may be applied; however, extra deprotection steps are required to obtain the benzoin product.

(1) (a) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Synthesis*; Wiley-VCH: Weinheim, Germany, 1997. (b) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, 1983; Chapter 2.
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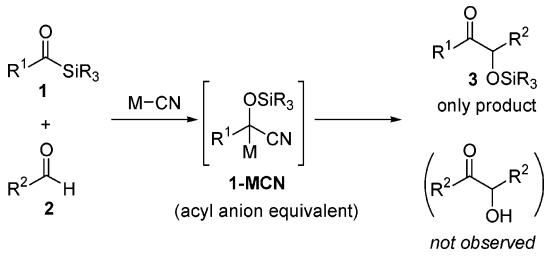
(5) Stetter, H.; Daembkes, G. *Synthesis* **1977**, 403−404.
(6) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328.
(7) For some congeners of the classic benzoin reaction, see: (a) Rozwadowska, M. D. *Tetrahedron* **1985**, *41*, 3135−3140. (b) Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fiorenza, M.; Rossini, G. *J. Org. Chem.* **1985**, *50*, 130−133. (c) Heck, R.; Henderson, A. P.; Kohler, B.; Retey, J.; Golding, B. T. *Eur. J. Org. Chem.* **2001**, 2623−2627. (d) Pohl, M.; Lingen, B.; Müller, M. *Chem.−Eur. J.* **2002**, *8*, 5288−5295. (e) Cunico, R. F. *Tetrahedron Lett.* **2002**, *43*, 355−358. (f) Demir, A. S.; Reis, O. *Tetrahedron* **2004**, *60*, 3803−3811. (g) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* **2004**, *346*, 1097−1100.
(8) For highly enantioselective homobenzoin reactions, see: Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743−1745.
(9) For an example of highly enantioselective enzyme-catalyzed aryl−aryl cross benzoin reactions, see: Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084−12085.
(10) Enantioselective cross silyl benzoin reactions have been reported: Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070−3071.
(11) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.
(12) Kuebrich, J. P.; Schowen, R. L.; Wang, M.-S.; Lupes, M. E. *J. Am. Chem. Soc.* **1971**, *93*, 1214−1220.
(13) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726.
(14) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699−702.
(15) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124−5131.
(16) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231−237.
(17) Groebel, B. T.; Seebach, D. *Synthesis* **1977**, 357−402.
(18) Hünig, S.; Wehner, G. *Synthesis* **1975**, 391−392.
(19) Hünig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062−2067.

Scheme 2. Cross Silyl Benzoin Additions Based on [1,2]-Brook Rearrangement



Since the formation of an acyl anion equivalent via the reaction of an aldehyde with cyanide ion or a thiazolium carbene is the key step in the benzoin and related[20] condensations, we speculated that regiocontrolled direct cross benzoin reactions may be achieved if alternative methods of acyl anion formation could place the reaction under kinetic control. In this context, in situ generation of (silyloxy)nitrile anions from acylsilanes by cyanide-promoted [1,2]-Brook rearrangement[21,22] appeared to have significant potential. The application of this particular silicon migration has been reported by several groups. Degl'Innocenti demonstrated that enones are acylated by acylsilanes under the influence of cyanide catalysis,[23] while Reich reported that cyanide triggers an addition/rearrangement/elimination sequence with an α-thiophenyl acylsilane.[24] Takeda's group has shown that (silyloxy)nitrile anions generated by the Brook rearrangement in the reaction of (*β*-(trimethylsilyl)-acryloyl)silane can undergo methylation at the *γ*-position.[25] Most recently, cyanide-catalyzed cyanation/1,2-Brook/acylation reactions of acylsilanes have been disclosed.[26−28] We anticipated that with cyanide as the catalyst, unsymmetrical α-silyloxy ketone products could be prepared by trapping (silyloxy)nitrile anions with aldehydes (Scheme 2). This projected application differs from the conceptually related fluoride-promoted acylsilane/aldehyde coupling reactions described by Degl'Innocenti and Heathcock: attack of F^- at silicon is thought to be crucial to the success of those additions.[29−31]

This article provides a full account of the development of a new cross silyl benzoin reaction, including improved reaction conditions and an evaluation of the mechanism.[32]

Results and Discussion

Development of a KCN/18-Crown-6 Catalytic System. KCN in combination with the phase transfer catalyst, 18-crown-6, is an effective reagent for cyanation of electrophilic substrates[33] and an effective catalyst for initiation of the Brook rearrangement.[25,26,28] Preliminary experiments indicated that KCN/18-crown-6 was also an effective catalyst system for silyl benzoin addition between benzoyl triethylsilane[34] and benzaldehyde. With 10 mol % 18-crown-6 and 0.3 equiv of KCN, silyl-protected benzoin adduct **3a-TES** (Table 1) can be obtained in 90% yield in an operationally convenient reaction time (2 h). Initial attempts to decrease the catalyst loading to 0.1 equiv of KCN led to a significant increase in reaction time (>12 h).

To evaluate the generality and regiospecificity of the silyl benzoin reaction, the substrate scope was studied using a variety of acylsilanes and aldehydes (Table 1). Reactions between aryl acylsilanes and aryl or heteroaromatic aldehydes gave good to excellent yields of α-silyloxy ketone products at ambient temperature (entries 1−11). The reaction times for all entries were similar (typically 1−5 h). Electron-poor and electron-rich substrates displayed little difference in reactivity. Significant steric demand was tolerated without a decrease in yield or an increase in reaction time (entry 10). The more challenging aryl−alkyl′ and alkyl−aryl′ benzoin adducts were obtained in moderate to good yields (entries 12−17). Easily prepared TMS (trimethylsilyl) and DMPS (dimethylphenylsilyl) acylsilanes[35,36] function analogously in the cross silyl benzoin addition; however, compared with the triethylsilyl group, the more labile groups were prone to desilylation during purification, and α-silyloxy ketone products were isolated in somewhat lower yields (entries 18 and 19). Either regioisomeric benzoin adduct can be prepared simply through judicious selection of the acylsilane and the aldehyde (cf. **3b-TES**/**3c-TES** (entries 2 and 3), **3d-TES**/**3e-TES** (entries 4 and 5), **3f-TES**/**3g-TES** (entries 6 and 7), **3h-TES/3i-TES** (entries 8 and 9), and **3p-TES/3q-TES** (entries 16 and 17). By way of comparison, thiazolium carbene-catalyzed benzoin reaction between benzaldehyde and isobutyraldehyde provides a 2:1 mixture of regioisomeric cross acyloins,[5] while the analogous cross silyl benzoin reaction gives only one isomer, **3l-TES** (entry 12). Benzoin reaction of *p*-anisaldehyde with benzaldehyde via cyanide catalysis allows access to only the thermodynamic isomer (hydroxyl derivative of **3e-TES**).[2] In contrast, entries 4 and 5 demonstrate that the kinetic control inherent in the acylsilane reaction circumvents this issue and provides access to both regioisomers.

Influence of Water on the Phase Transfer Process and Development of More Practical Reaction Conditions. We presumed that the (silyloxy)nitrile anion intermediates (**1-MCN**, Scheme 2) of the cross silyl benzoin reaction would be sensitive to water. This moisture sensitivity problem has been addressed in our previous studies of the cyanation/1,2-Brook/acylation of acylsilanes;[26,27] therefore, the reactions in Table 1 were conducted in dry solvent under an inert atmosphere. While yields were always the same for a given acylsilane/aldehyde pair, the reaction times were not reproducible (normally, from 1 to 5 h with 0.3 equiv of KCN/18-crown-6). We also noticed that

(20) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696−9697.
(21) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84.
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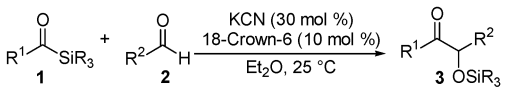
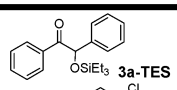
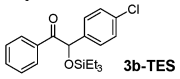
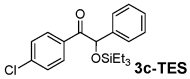
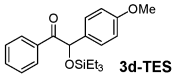
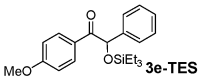
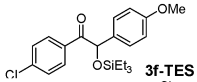
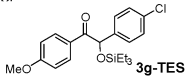
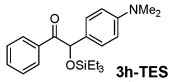
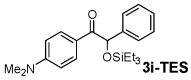
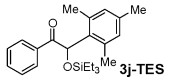
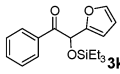
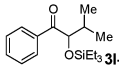
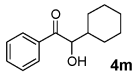
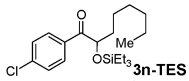
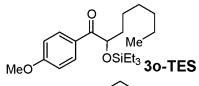
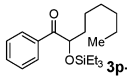
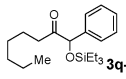
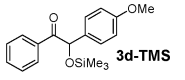
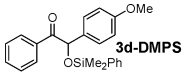
(29) Schinzer, D.; Heathcock, C. H. *Tetrahedron Lett.* **1981**, *22*, 1881−1884.
(30) Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fiorenza, M.; Rossini, G. *J. Org. Chem.* **1985**, *50*, 130−133.
(31) Degl'Innocenti, A.; Pike, S.; Walton, D. R. M.; Seconi, G.; Ricci, A.; Fiorenza, M. *J. Chem. Soc., Chem. Commun.* **1980**, 1201−1202.
(32) A portion of this work has been communicated: (a) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534−2536. (b) Bausch, C. C.; Johnson, J. S. *J. Org. Chem.* **2004**, *69*, 4283−4285.
(33) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929−4932.
(34) Acyl triethylsilanes were prepared in three steps from the corresponding aldehydes. For detailed information, see the Supporting Information of ref 26.
(35) Benzoyl trimethylsilane was prepared by reductive silylation of methyl benzoate. For detailed information, see: Tongco, E. C.; Wang, Q.; Prakash, G. K. S. *Synth. Commun.* **1997**, *27*, 2117−2123.
(36) Acyl dimethylphenylsilanes were prepared by reductive lithiation of chlorodimethylphenyl silane, transmetalation, and addition to acid chlorides. For detailed information, see: Bonini, B. F.; Comesfranchini, M.; Mazzanti, G.; Passamonti, U.; Ricci, A.; Zani, P. *Synthesis* **1995**, 92−96.

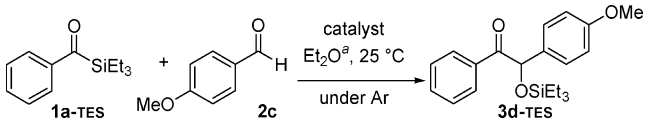
Table 1. Cross Silyl Benzoin Additions of Acylsilanes and Aldehydes Catalyzed by KCN/18-Crown-6[a]



entry	1	R^2	product	yield (%)[b]
1	$PhCOSiEt_3$ (**1a-TES**)	Ph (**2a**)	 **3a-TES**	90
2	$PhCOSiEt_3$ (**1a-TES**)	4-ClPh (**2b**)	 **3b-TES**	82
3	4-$ClPhCOSiEt_3$ (**1b-TES**)	Ph (**2a**)	 **3c-TES**	86
4	$PhCOSiEt_3$ (**1a-TES**)	4-MeOPh (**2c**)	 **3d-TES**	79
5	4-$MeOPhCOSiEt_3$ (**1c-TES**)	Ph (**2a**)	 **3e-TES**	85
6	4-$ClPhCOSiEt_3$ (**1b-TES**)	4-MeOPh (**2c**)	 **3f-TES**	80
7	4-MeOPhCOSiEt_3 (**1c-TES**)	4-ClPh (**2b**)	 **3g-TES**	80
8	$PhCOSiEt_3$ (**1a-TES**)	4-Me_2NPh (**2d**)	 **3h-TES**	66[c]
9	4-Me_2NPhCOSiEt_3 (**1d-TES**)	Ph (**2a**)	 **3i-TES**	95[c]
10	$PhCOSiEt_3$ (**1a-TES**)	Mesityl (**2e**)	 **3j-TES**	85
11	$PhCOSiEt_3$ (**1a-TES**)	2-furyl (**2f**)	 **3k-TES**	75
12	$PhCOSiEt_3$ (**1a-TES**)	*i*-propyl (**2g**)	 **3l-TES**	66
13	$PhCOSiEt_3$ (**1a-TES**)	cyclohexyl (**2h**)	 **4m**	94[d]
14	4-$ClPhCOSiEt_3$ (**1b-TES**)	*n*-hexyl (**2i**)	 **3n-TES**	75
15	4-$MeOPhCOSiEt_3$ (**1c-TES**)	*n*-hexyl (**2i**)	 **3o-TES**	51
16	$PhCOSiEt_3$ (**1a-TES**)	*n*-hexyl (**2i**)	 **3p-TES**	70
17	*n*-$HexCOSiEt_3$ (**1e-TES**)	Ph (**2a**)	 **3q-TES**	51[e]
18	$PhCOSiMe_3$ (**1a-TMS**)	4-MeOPh (**2c**)	 **3d-TMS**	67[f]
19	$PhCOSiMe_2Ph$ (**1a-DMPS**)	4-MeOPh (**2c**)	 **3d-DMPS**	63[f]

[a] $R^1C(O)SiR_3$ (1.0 equiv), R^2CHO (1.1 equiv), 18-crown-6 (0.1 equiv), and KCN (0.3 equiv) in Et_2O at 25 °C for 1−5 h, unless otherwise noted. See Supporting Information for details. [b] Isolated yield of analytically pure material. [c] Reaction time = 10 h. [d] [18-Crown-6·K]CN complex (0.2 equiv); the silyloxy ketone product was subjected to deprotection with 1 M HCl in MeOH. [e] $R^1C(O)SiR_3$ (1.0 equiv), R^2CHO (4.0 equiv), 18-crown-6 (0.3 equiv), and KCN (0.5 equiv) in Et_2O at 25 °C. [f] [18-Crown-6·K]CN complex (0.1 equiv).

Table 2. Influence of Water on the Phase Transfer Process



entry	catalyst	added H_2O (equiv)[b]	time	yield (%)[c]
1	KCN/18-crown-6 (30 mol %)	0	5 h	79
2	KCN/18-crown-6 (10 mol %)	0	24 h	76
3	KCN/18-crown-6 (10 mol %)	2	6 h	83
4	KCN/18-crown-6 (10 mol %)	10	3 h	75
5	KCN/18-crown-6 (10 mol %)	20	3 h	70
6	KCN/18-crown-6 (10 mol %)	excess[d]	24 h	low conversion
7	[18-crown-6·K]CN[e] (10 mol %)	0	<10 min	74

[a] Et_2O (10 mL) was dried by passage through a bed of activated Al_2O_3 under Ar. [b] Equiv of H_2O relative to KCN. [c] Isolated yield of analytically pure material. [d] A 2:1 Et_2O/H_2O biphase was employed. [e] [18-Crown-6·K]CN complex was prepared by the literature method (ref 37).

reactions sealed with new septa required longer reaction times than those sealed with used septa. Those observations led us to believe that trace amounts of water may not halt catalysis by quenching **1-MCN**; on the contrary, water could increase the reaction rate by facilitating the phase transfer process. Several test reactions between benzoyl triethylsilane (**1a-TES**) and *p*-anisaldehyde (**2c**) were designed to evaluate the effect of H_2O; the results are summarized in Table 2.

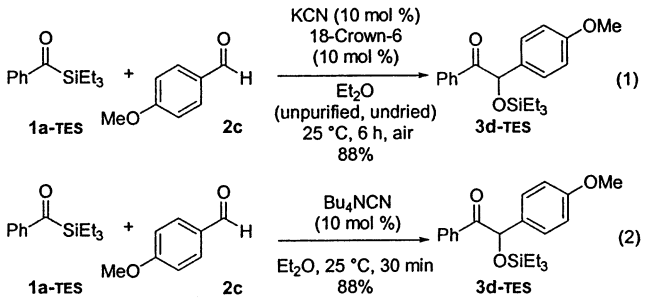
All experiments were performed in oven-dried flasks sealed by new septa, and dry Et_2O was obtained from an activated alumina column.[38] Under anhydrous conditions, the reaction with 30 mol % KCN and 30 mol % 18-crown-6 was complete in 5 h in 79% yield (entry 1), while the reaction using 10 mol % catalyst required 24 h and afforded a slightly lower yield (entry 2). By introducing 20 mol % H_2O, the reaction time dropped to 6 h (10 mol % catalyst), while the yield increased from 76 to 83% (entry 3). The addition of more H_2O (100 mol %) resulted in further reduction of the reaction time (from 6 to 3 h), but no further change was observed with 200 mol % H_2O (entries 4 and 5). The role of water in solid−liquid phase transfer catalysis of KCN has been studied by Liotta and co-workers.[39] They observed similar results in the reaction of benzyl halides with KCN in the presence of 18-crown-6: small amounts of added water resulted in a significant rate enhancement. They postulated that water added to the solid−liquid system could coat the surface of the solid particles to form a third phase that was termed the omega phase. This third phase consists of water, "dissolved" KCN, organic solvent, and crown ether extracted from organic phase. The complexation of KCN by 18-crown-6 occurs in the omega phase. It was proposed that in the absence of added water, the mass transfer of KCN from the solid phase directly into the organic phase is slow and becomes the limiting step of the reaction, while in the presence of small amounts of

(37) Livinghouse, T. *Org. Synth.* **1981**, *60*, 126−132.
(38) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Educ.* **2001**, *78*, 64.
(39) Liotta, C. L.; Berkner, J.; Wright, J.; Fair, B. ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; pp 29−40.

added water, the omega phase is an integral part of the reaction system and the mass transfer of the complex into the organic phase is faster.

Attempts to carry out the reaction under liquid−liquid biphase conditions failed to give appreciable product (entry 6), probably due to an unfavorable partition coefficient. Since KCN and 18-crown-6 eventually form [18-crown-6·K]CN, we speculated that the catalytic reaction may be more efficient with a preformed complex. Since [18-crown-6·K]CN[37] has appreciable solubility in Et_2O, the solid−liquid biphasic reaction was converted to a homogeneous catalytic process. The reaction time with 10 mol % of this complex decreased dramatically to less than 10 min in the absence of water (entry 7). This suggested that in the presence of water and without the preformed complex, steps involving the mass transfer of $KCN_{(s)}$ from the solid phase to the omega phase and complexation of $KCN_{(\omega)}$ by 18-crown-6 were still rate limiting.

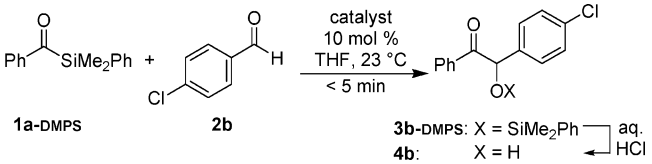
Considering the effect of water on phase transfer catalysis, we expected to develop a more practical and efficient cross silyl benzoin reaction. Taking advantage of a trace amount of water in unpurified Et_2O, α-silyloxy ketone can be obtained in 88% yield with 10 mol % catalyst loading (eq 1). The reaction is complete in an operationally convenient time (6 h) and can be performed without the need for an inert atmosphere. Tetrabutylammonium cyanide, which is commercially available or easily prepared from NaCN and a cheaper phase transfer catalyst, tetrabutylammonium bisulfate,[40] is an alternative catalyst for the cross benzoin reaction. Within 30 min, the reaction with 10 mol % catalyst loading afforded **3d-TES** in 88% yield (eq 2).



Development of a $La(CN)_3$ Catalytic System. Although the substrate scope of KCN/18-crown-6-catalyzed cross silyl benzoin additions was reasonable for aryl−aryl′ combinations, the reaction produced lower yields for alkyl−aryl′ or aryl−alkyl′ adducts and afforded <20% alkyl−alkyl′ products. We wondered if a transition metal counterion could provide a more tolerant catalyst. To enhance the reactivity of both aromatic and aliphatic substrates and to further provide a platform for the development of enantioselective variants, transition metal cyanides were examined as new catalysts for the cross silyl benzoin reaction.

The recent observation that (salen)Al−CN complexes react with acylsilanes to give (silyloxy)nitrile anions (**1-MCN**, M = Al(salen)) led us to consider these complexes as potential catalysts,[27] but our efforts in this area were not fruitful (entry 1). A possible reason for the absence of catalysis will be discussed in the context of our mechanistic studies (vide infra). Attempts employing lanthanum *i*-propoxides activated by Me_3-SiCN failed to provide reproducible results (entries 2 and 3); however, $Ln(CN)_3$ generated from $(n\text{-Bu})_3Ln/Me_3SiCN$ was found to be an effective catalyst and provided consistent yields.[41,42] According to the Utimoto protocol,[41] $LaCl_3$ (0.1 equiv) was treated with *n*-butyllithium (0.3 equiv) to give a tributyllanthanum species, which upon subsequent addition of Me_3SiCN, provided the active catalyst. Six different (cyanide)-lanthanum catalysts were evaluated in the reaction between benzoyl dimethylphenylsilane (**1a-DMPS**) and 4-chlorobenzaldehyde (**2b**); the results are summarized in Table 3. All catalysts were generated in situ, and the starting materials **1a-DMPS** and **2b** were added to the catalyst suspension. While all of the Ln-$(CN)_3$ complexes delivered the desired α-hydroxy ketone **4b** (after acidic workup), $La(CN)_3$ afforded the highest yield (entry 6).

Table 3. Evaluation of $M(CN)_n$ Complexes as Cross Silyl Benzoin Catalysts



entry	catalyst	yield[a](%)
1	(salen)Al−CN	0
2	$Er(i\text{OPr})_3/Me_3SiCN$	42−66
3	$Yb(i\text{OPr})_3/Me_3SiCN$	30−55
4	$Ce(CN)_3$[b]	40
5	$Er(CN)_3$[b]	50
6	$La(CN)_3$[b]	75
7	$Sm(CN)_3$[b]	51
8	$Y(CN)_3$[b]	5
9	$Yb(CN)_3$[b]	68

[a] Isolated yield of **4b**. [b] Catalyst prepared via treatment of 0.1 equiv of $(n\text{-Bu})_3M$ with 0.3 equiv of Me_3SiCN (see text).

With the optimized catalyst in hand, the scope of the cross benzoin reaction was further studied (Table 4). From our earlier experience that the more labile TMS (trimethylsilyl) and DMPS (dimethylphenylsilyl) groups underwent some desilylation during purification, all substrates that contained those two silyl groups were subjected to silyl ether deprotection with aqueous HCl upon completion of the reaction. Compared with the KCN/18-crown-6-catalyzed cross benzoin reaction, $La(CN)_3$ typically catalyzed the reactions in less than 5 min (cf. 1−5 h for reactions with KCN/18-crown-6). The $La(CN)_3$ catalyst gave yields comparable to those of the KCN/18-crown-6 catalyst previously reported for aryl−aryl′ benzoin adducts (entries 1−3, 6, and 7). The $La(CN)_3$ system gave excellent yields in coupling $PhCOSiEt_3$ and heteroaromatic aldehydes (entries 4 and 5). $PhCOSiMe_3$ underwent selective catalyzed 1,2-addition to an α,β-unsaturated aldehyde (entry 8). Aliphatic aldehydes, including those that are α-branched (cyclohexane carboxaldehyde, entry 10) and *tert*-alkyl (pivaldehyde, entry 11), are also effective acceptor substrates. It is noteworthy that the latter aldehyde is completely unreactive in the KCN/18-crown-6 system.

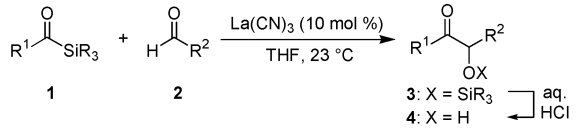
A significant improvement has been observed for alkyl−aryl′ and alkyl−alkyl′ benzoin adducts. In our previous report, catalyst loading and electrophile concentration had to be

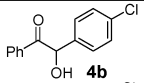
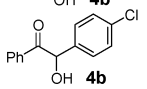
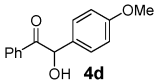
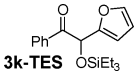
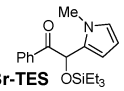
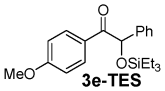
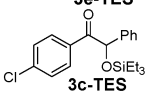
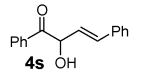
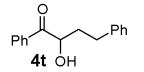
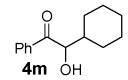
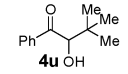
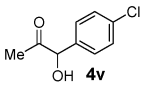
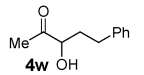
(40) Dehmlow, E. V.; Kunesch, E. *Liebigs Ann. Chem.* **1985**, 1904−1909.

(41) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209−6212.

(42) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004.

Table 4. Catalyzed Silyl Benzoin Addition Reactions of Acylsilanes and Aldehydes[a]



entry	1	R^2	product	yield (%)[b]
1[c]	PhCOSiMe$_2$Ph (**1a-DMPS**)	4-ClPh (**2b**)	 **4b**	75
2[c]	PhCOSiMe$_3$ (**1a-TMS**)	4-ClPh (**2b**)	 **4b**	87
3[c]	PhCOSiMe$_3$ (**1a-TMS**)	4-MeOPh (**2c**)	 **4d**	81
4	PhCOSiEt$_3$ (**1a-TES**)	2-furyl (**2f**)	 **3k-TES**	88
5	PhCOSiEt$_3$ (**1a-TES**)	*N*-Me-2-pyrroyl (**2j**)	 **3r-TES**	93
6	4-MeOPhCOSiEt$_3$ (**1c-TES**)	Ph (**2a**)	 **3e-TES**	84
7	4-ClPhCOSiEt$_3$ (**1b-TES**)	Ph (**2a**)	 **3c-TES**	83
8[c]	PhCOSiMe$_3$ (**1a-TMS**)	(*E*)-CH=CHPh (**2k**)	 **4s**	50[d]
9[c]	PhCOSiMe$_3$ (**1a-TMS**)	CH$_2$CH$_2$Ph (**2l**)	 **4t**	64[d]
10[c]	PhCOSiEt$_3$ (**1a-TES**)	cyclohexyl (**2h**)	 **4m**	85[d]
11[c]	PhCOSiEt$_3$ (**1a-TES**)	*t*-Bu (**2m**)	 **4u**	66[d]
12[c]	MeCOSiMe$_3$ (**1f-TMS**)	4-ClPh (**2b**)	 **4v**	70[d]
13[c]	MeCOSiMe$_3$ (**1f-TMS**)	CH$_2$CH$_2$Ph (**2l**)	 **4w**	48[d]

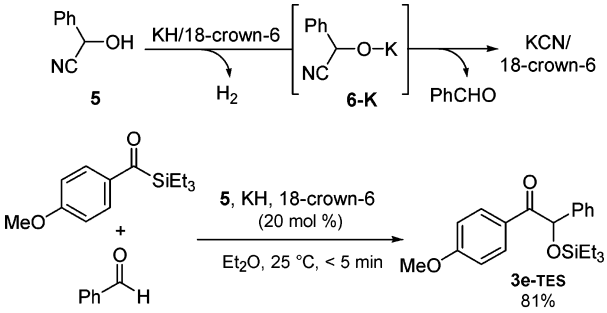
[a] $R^1C(O)SiR_3$ (1.0 equiv), R^2CHO (1.1 equiv), and $La(CN)_3$ (0.1 equiv) in THF at 25 °C for <5 min, unless otherwise noted. See Supporting Information for details. [b] Yield of isolated analytically pure material. [c] The silyloxy ketone product was subjected to deprotection with 1 M HCl in MeOH. [d] $R^1C(O)SiMe_3$ (1.0 equiv), R^2CHO (1.5 equiv), and $La(CN)_3$ (0.1 equiv) in THF at 25 °C for 15 min.

significantly increased to achieve satisfactory yields. $La(CN)_3$ catalyzes the silyl benzoin reaction of acetyl trimethylsilane and 4-chlorobenzaldehyde in reasonable yield (entry 12), and for the first time that we are aware, cyanide catalysis has proven effective (albeit in a modest yield) for the synthesis of an alkyl−alkyl′ acyloin (entry 13).

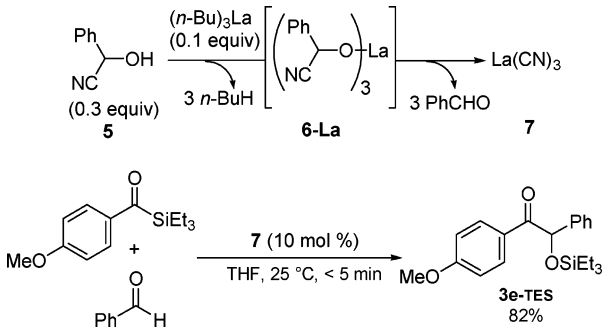
Mechanism of the Cross Silyl Benzoin Addition. (A) Evaluation of Potential Competing Reactions. The initiating step of the classic benzoin reaction is aldehyde cyanation, while the cross silyl benzoin reaction relies on productive cyanation of the acylsilane at the onset of the catalytic cycle. Because aldehydes are more electrophilic than acylsilanes, successful catalysis of the cross silyl benzoin reaction is dependent on *reversible* and *nonproductive* aldehyde cyanation: the derived alkoxide products, **6-K** and **6-La**, cannot be stable. If aldehyde cyanation were irreversible, those alkoxides would become a nonproductive shunt of metal cyanide catalysts and acylsilane cyanation would be impossible. The absence of benzoin catalysis with (salen)Al−CN complexes (Table 3, entry 1) is an example where a stable tetrahedral intermediate sequesters a metal cyanide that has been previously demonstrated to react with acylsilanes.

(i) Aldehyde Cyanation. To assess the reversibility of aldehyde cyanation in both KCN/18-crown-6- and $La(CN)_3$-catalyzed cross silyl benzoin reactions, mandelonitrile (**5**) was employed as a catalyst precursor in conjunction with bases that would furnish the appropriate counterion, KH or $(n\text{-Bu})_3La$, respectively. In the KCN/18-crown-6 system, the reaction between KH and the cyanohydrin should be rapid and irreversible to generate alkoxide **6-K**. If aldehyde cyanation is reversible, benzaldehyde extrusion should yield the competent catalyst KCN. In the test experiment, after KH and 18-crown-6 were introduced to an Et_2O solution of PhCH(OH)CN, (*p*-MeOPh)$COSiEt_3$, and PhCHO, the cross benzoin reaction was complete within 5 min. The desired α-silyloxy ketone product, (*p*-MeOPh)COCH($OSiEt_3$)Ph (**3e-TES**), was obtained in 81% yield (Scheme 3). Analogously, $La(CN)_3$ can be generated by treating

Scheme 3. Test for Reversibility of Aldehyde Cyanation (KCN/18-Crown-6 System)

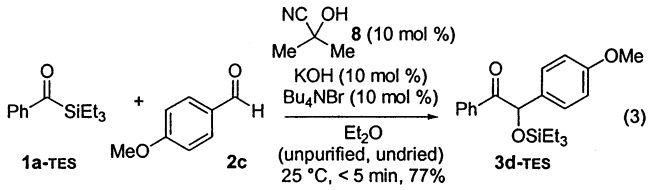


Scheme 4. Test for Reversibility of Aldehyde Cyanation ($La(CN)_3$ System)



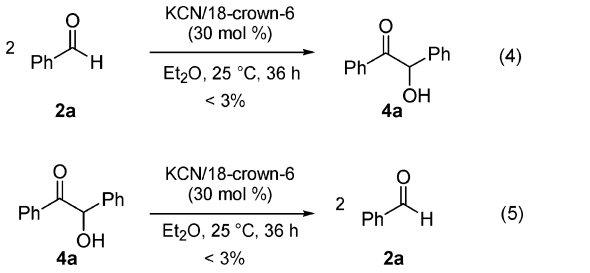
a THF solution of PhCH(OH)CN with a solution of freshly prepared $(n\text{-Bu})_3La$. After introducing a THF solution of (*p*-MeOPh)$COSiEt_3$ and PhCHO, the cross silyl benzoin product, **3e-TES**, was isolated in 82% yield (Scheme 4). Both results were consistent with our working hypothesis.

These results further suggested a practical improvement in executing the catalyzed reactions. Acetone cyanohydrin (**8**) is a latent source of $^{-}$CN that is cheap, stable, and easily handled. After $PhCOSiEt_3$ **1a-TES** and *p*-anisaldehyde **2c** were mixed with acetone cyanohydrin **8** (0.1 equiv) and Bu_4NBr (0.1 equiv) in the presence of powdered KOH (0.1 equiv), α-silyloxy ketone product **3d-TES** can be obtained in 77% yield within 5 min (eq 3). This represents an operationally simple and economically attractive method of catalysis.



(ii) Aldehyde Dimerization. The classic benzoin condensation is conducted in warm alcohol solvent.[2] A control experiment showed that under typical cross silyl benzoin reaction conditions (Et_2O, ambient temperature), benzoin (**4a**) was not observed over extended periods of time (eq 4 in Scheme 5). To verify

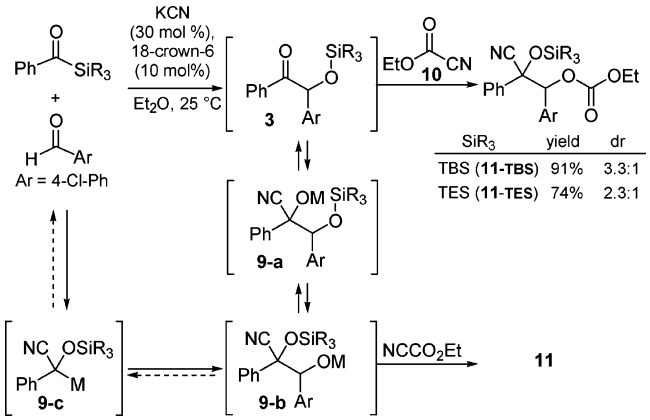
Scheme 5. Test for Competing Homobenzoin Reaction under Cross Silyl Benzoin Addition Conditions



that benzoin is not formed reversibly, **4a** was subjected to normal cross silyl benzoin conditions (eq 5 in Scheme 5). The absence of benzaldehyde further indicates that no productive chemistry arises from aldehyde cyanation under the mild reaction conditions employed.

(B) Tandem Silyl Benzoin Addition/Cyanation/O-Acylation and Underlying Mechanistic Information. The cross silyl benzoin addition has been coupled to a second C−C bond construction that occurs in the same reaction pot (Scheme 6).

Scheme 6. Sequential One-Pot Silyl Benzoin Addition/Cyanation/O-Acylation Reaction



Thus, benzoyl *tert*-butyldimethylsilane and *p*-chlorobenzaldehyde participate in a KCN/18-crown-6-catalyzed silyl benzoin reaction. Upon consumption of the acylsilane (TLC analysis), ethyl cyanoformate (**10**) was added. The α-silyloxy ketone intermediate (**3**) underwent a subsequent catalyzed cyanation, 1,4-silyl migration, and O-acylation with ethyl cyanoformate to afford silyl cyanohydrin carbonate **11-TBS** in 91% yield as a single regioisomer (d.r. = 3.3:1, relative stereochemistry unassigned). The analogous reaction between benzoyl triethylsilane and *p*-chlorobenzaldehyde affords TES-cyanohydrin carbonate **11-TES** in 74% yield as a single regioisomer (d.r. = 2.3:1, relative stereochemistry unassigned). Conveniently, orthogonal protection of the product's two carbinol groups is an inherent characteristic of the reaction.

Due to the migration of the silyl group between two adjacent oxygen atoms of the intermediates **9-a** and **9-b** (Scheme 6), both intermediates can, in principle, react with cyanoformate, and two possible regioisomers could be obtained; however, only the regioisomer derived from acylation of **9-b** was observed.[43] The deactivating geminal nitrile group and steric congestion associated with alkoxide **9-a** apparently renders the tertiary site unreactive. Equilibration via 1,4-silyl migration is clearly faster than acylation of **9-a**, and the more nucleophilic secondary alkoxide **9-b** reacts with cyanoformate to give the observed regioisomer.

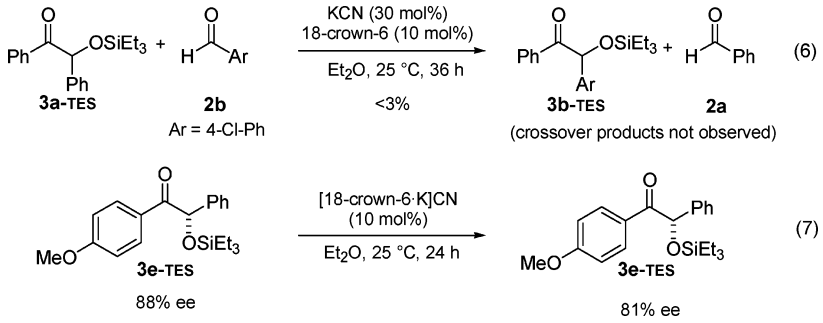
The new tandem reaction provided us with a useful piece of mechanistic information: the last two steps of cross silyl benzoin addition are reversible.[44] At this stage, there were two questions left to obtain the integrated catalytic cycle information: (1) Does the intermediate **9-b** undergo C−C bond cleavage during the reaction process (**9-b** → **9-c**)? (2) Are acylsilane cyanation and [1,2]-Brook rearrangement reversible under the reaction conditions, that is, is **9-c** formed reversibly?

(C) Evaluating Reversibility of the C−C Bond Forming Step. Because of our interest in the development of enantioselective silyl benzoin reactions,[10] we were concerned about the reversibility of C−C bond formation. We designed two crossover experiments to investigate this point. On the basis of ^{1}H NMR analysis, the reaction between triethylsilyloxy phenyl acetophenone (**3a-TES**) and *p*-chlorobenzaldehyde (**2b**) under standard conditions afforded none of the crossover product **3b-TES** over 36 h (eq 6 in Scheme 7). If C−C bond cleavage had occurred, (silyloxy)nitrile anion **9-c** would have been generated and aldehyde **2b** would have been incorporated to give the crossover product **3b-TES**, a compound that we have fully characterized. The absence of **3b-TES** confirms that **9-b** and **9-c** are not in equilibrium. This conclusion was verified by a second experiment in which enantiomerically enriched silyloxy benzoin **3e-TES** was treated with 10 mol % [18-crown-6·K]-CN for an extended period of time (eq 7 in Scheme 7). The fact that the reaction only gave slightly diminished enantiomeric excess over 24 h indicated that on the time scale of the reaction, racemization is negligible and C−C bond formation is irreversible. Base-catalyzed racemization via enolization is also discounted by this experiment.

(43) Details of the regiochemical proof can be found in the Supporting Information.

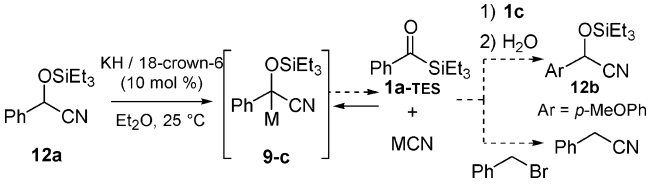
(44) A reviewer correctly pointed out that this experiment suggests, but does not definitively verify, reversibility of the retrocyanation and silyl migration under the silyl benzoin conditions since we have introduced a new variable (i.e., presence of ethyl cyanoformate). We agree that the probability that these equilibria are "turned on" only in the presence of ethyl cyanoformate is small, but not zero.

Scheme 7. Test for Reversibility of C−C Bond Formation



(D) Interrogating the Reversibility of Acylsilane Cyanation and [1,2]-Brook Rearrangement. Hünig and co-workers reported lithiation of phenyl trimethylsilyloxy cyanohydrin **12a** followed by addition to aldehydes to form unsymmetrical benzoins.[18,19] Intermediate **9-c** (M = Li) is inferred as the key nucleophilic species. We wished to synthesize the proposed intermediate **9-c** (M = [18-crown-6·K]) via an analogous method. Phenyl silyloxy cyanohydrin **12a** was treated by KH in the presence of 18-crown-6 (Scheme 8) in an effort to generate (silyloxy)nitrile anion **9-c** in the same environment as it is formed in the cross silyl benzoin reaction. If reverse Brook (silyl-Wittig) rearrangement[45,46] and retrocyanation occur, $^{-}$CN and acylsilane **1a-TES** would be formed. We attempted to verify the generation of acylsilane **1a-TES** by ^{1}H NMR spectroscopy, but in no case were we able to observe its NMR signatures. We sought indirect evidence by trapping the generated $^{-}$CN with other electrophiles; however, neither the reaction with *p*-methoxybenzoyl triethylsilane (aqueous workup) nor the reaction with benzyl bromide afforded the expected products. Both reactions showed only undefined decomposition of the starting material **12a**; again, acylsilane **1a-TES** was not observed. At this time, we cannot conclude whether **9-c** is formed reversibly under the reaction conditions.

Scheme 8. Test for Reversibility of Cyanation/Brook Rearrangement Steps



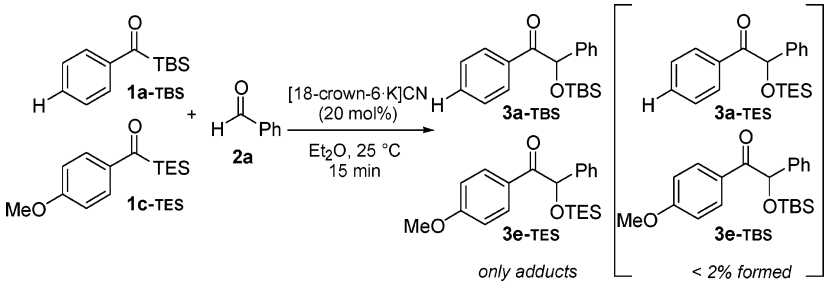
(E) Test for Silyl Group Transfer Pathway. Since traditional benzoin reactions are run in ethanol, the proton-transfer steps could proceed through an intramolecular and/or intermolecular pathway. In the cross silyl benzoin addition, silyl transfer takes the place of proton transfer, and the reaction proceeds in aprotic solvent. To provide experimental support for the proposed mechanism, it was deemed critical to establish the nature of the silyl group transfer. A simple crossover experiment was designed (Scheme 9); two acylsilanes, benzoyl *tert*-butyldimethylsilane (**1a-TBS**) and *p*-methoxybenzoyl triethylsilane (**1c-TES**), which are differentiated in the identity of both the aryl and silyl groups, underwent reaction with a single aldehyde (**2a**, 2 equiv) under normal cross silyl benzoin conditions. The product distribution was evaluated by ^{1}H NMR spectroscopy. Only **3a-TBS** and **3e-TES** were observed, confirming the intramolecular silyl group transfer pathway.

Proposed Catalytic Cycle for Cross Silyl Benzoin Additions. The collected mechanistic information allows us to derive a reasonable catalytic cycle for cross silyl benzoin additions (Scheme 10). Aldehyde cyanation occurs, but is neither productive nor irreversible; therefore, cyanide is not sequestered and is available to undergo nucleophilic addition to acylsilane **1**, followed by [1,2]-Brook rearrangement to yield (silyloxy)-nitrile anion **9-c**. There was no direct evidence for the reversibility of those two steps. The cross silyl benzoin reaction is *regiospecific* by virtue of an irreversible carbon−carbon bond forming step. The silyl group shuttles between two adjacent oxygen atoms in intermediates **9-b** and **9-a**, the latter of which reversibly releases the metal cyanide catalyst and leads to the desired product.

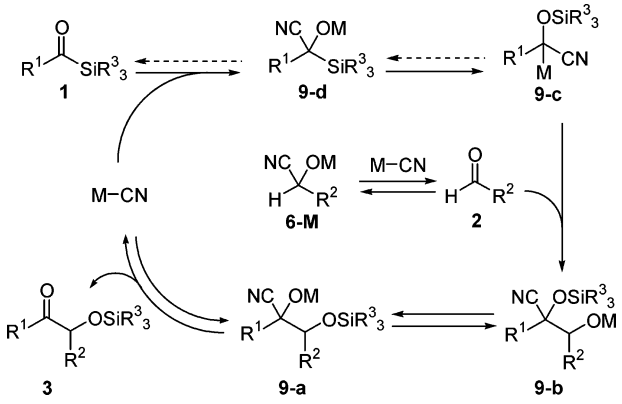
Conclusions

A new cross silyl benzoin addition reaction with complete regiochemical control has been developed to generate α-silyloxy ketone products. The KCN/18-crown-6 catalyst system can afford good to excellent yields for aryl and heteroaryl substrates. The scope was extended to alkyl and α,β-unsaturated substrates with an improved $La(CN)_3$ catalyst. Operationally simple reaction conditions were discovered that allow the alkali cyanide-catalyzed reactions to be conducted under ambient

Scheme 9. Test for Silyl Group Transfer Pathway



Scheme 10. Proposed Mechanism for Cross Silyl Benzoin Addition



conditions (rt, air). A tandem silyl benzoin addition/cyanation/O-acylation reaction that resulted in two new C−C bonds was achieved in excellent yields. Finally, the catalytic cycle of cross silyl benzoin additions was proposed based on detailed mechanistic studies.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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