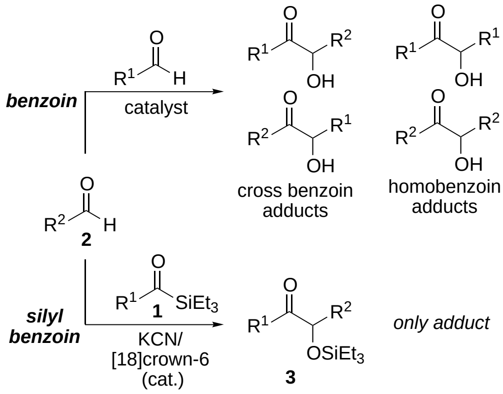
Selective Benzoin Condensation

Kinetic Control in Direct α-Silyloxy Ketone Synthesis: A New Regiospecific Catalyzed Cross Silyl Benzoin Reaction**

*Xin Linghu and Jeffrey S. Johnson**

Dedicated to Professor Maurice Brookhart
on the occasion of his 60th birthday

The benzoin condensation remains arguably the most direct method for synthesis of α-hydroxy ketones and is the quintessential reaction of an acyl anion equivalent. The utility of the traditional benzoin condensation is well documented, but its principal limitation arises in the coupling of two different aldehydes: the product distribution of the cross benzoin condensation is generally determined by the relative stability of the four possible products (Scheme 1).[1] The usual consequences of this energetic constraint are product mixtures or lack of access to the higher energy regioisomer. Since generation of an acyl anion equivalent in situ by the reaction of an aldehyde with cyanide ion or a thiazolium ylide is the key step in the benzoin and related condensations,[2–6] we speculated that alternative methods of acyl anion formation that place the reaction under kinetic control might circumvent the aforementioned limitations.[7] In this context, the generation of silyloxy nitrile anions from acylsilanes by cyanide-promoted [1,2] Brook rearrangement of acylsilanes was particularly intriguing.[8–10] Phase-transfer-catalyzed alkylation[11,12] and acylation[13] reactions of these species are known, but the analogous carbonyl addition reactions[14,15] under catalytic conditions have not been reported to the best of our knowledge. The purpose of this paper is to document new catalyzed silyl benzoin addition reactions of acylsilanes **1** and aldehydes **2** that facilitate complete regiochemical control in direct α-silyloxy ketone synthesis (Scheme 1).



Scheme 1. Benzoin and silyl benzoin addition reactions.

Preliminary experiments indicated that KCN/[18]crown-6 is an effective catalyst[16] for the silyl benzoin addition between benzoyl triethylsilane and benzaldehyde. An operationally convenient reaction time (2 h) was realized with 10 mol% [18]crown-6 and 0.3 equiv KCN. The reaction was possible with less catalyst (e.g., 0.1 equiv KCN); however, the reaction time increased to 12 h. To evaluate the generality of the silyl benzoin reaction, the substrate scope was studied by using a variety of acylsilanes and aldehydes (Table 1).

Collectively, the catalyzed reactions between aryl acylsilanes and aryl or heterocyclic aldehydes gave good to excellent yields of the product α-silyloxy ketones at ambient temperature (Table 1, entries 1–11). Most reaction times were less than 3 h. Electronically diverse substrates were tolerated and displayed little difference in reactivity. A sterically demanding substrate reacted without a decrease in yield or increase in reaction time (entry 10). The more challenging aryl–alkyl′ and alkyl–aryl′ benzoin adducts were obtained in moderate to good yields (entries 12–16). Efforts to synthesize alkyl–alkyl′ acyloins possessing enolizable protons on both reaction partners have to date been low yielding.

There are several noteworthy features of the silyl benzoin addition. First, the nascent secondary hydroxy group is protected as its derived silyl ether in situ. Second, no competing homobenzoin adducts are observed. Finally, either regioisomeric benzoin adduct may be prepared simply through judicious selection of the acylsilane and aldehyde (cf. **3b**/**3c** in entries 2 and 3, **3d**/**3e** in entries 4 and 5, **3f**/**3g** in entries 6 and 7, **3h**/**3i** in entries 8 and 9, and **3o**/**3p** in entries 15 and 16). By way of comparison, thiazolium-ylide-catalyzed benzoin reaction between benzaldehyde and isobutyraldehyde provides a 2:1 mixture of regioisomeric cross acyloins,[17] while the analogous cross silyl benzoin reaction gives only one isomer, **3l** (entry 12). Benzoin reaction of *p*-

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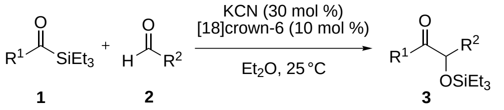
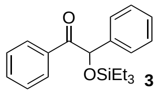
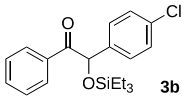
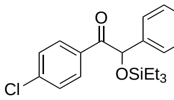
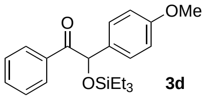
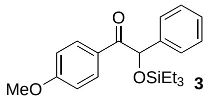
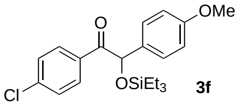
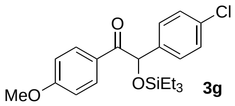
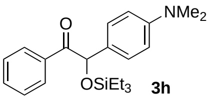
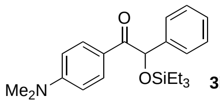
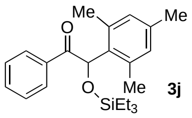
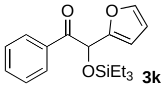
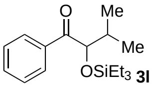
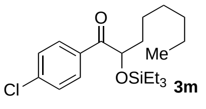
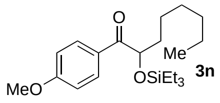
Table 1: Catalyzed silyl benzoin addition reactions of acylsilanes and aldehydes.[a]



Entry	R^1	R^2	Product	Yield [%][b]
1	Ph	Ph	 3a	90
2	Ph	4-ClPh	 3b	82
3	4-ClPh	Ph	 3c	86
4	Ph	4-MeOPh	 3d	79
5	4-MeOPh	Ph	 3e	85
6	4-ClPh	4-MeOPh	 3f	80
7	4-MeOPh	4-ClPh	 3g	80
8	Ph	4-Me$_2$NPh	 3h	66[c]
9	4-Me$_2$NPh	Ph	 3i	95[c]
10	Ph	mesityl	 3j	85
11	Ph	2-furyl	 3k	75
12	Ph	isopropyl	 3l	66
13	4-ClPh	*n*-hexyl	 3m	75
14	4-MeOPh	*n*-hexyl	 3n	51

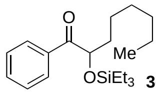
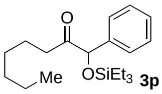
anisaldehyde with benzaldehyde under cyanide catalysis allows access to only the thermodynamic isomer (hydroxy derivative of **3e**).[1] In contrast, entries 4 and 5 demonstrate that the kinetic control inherent in the acylsilane reaction circumvents this issue and provides access to both regioisomers.

To account for the observed results, a silyl version of the Lapworth–Schowen benzoin condensation mechanism is proposed in Scheme 2.[2,18] Nucleophilic addition of a metal cyanide to acylsilane **1** generates the tetrahedral intermediate **1a,** which undergoes a [1,2] Brook rearrangement to afford the siloxy nitrile anion intermediate **1b**.[19] Addition to aldehyde **2** followed by 1,4-silyl migration gives alkoxide intermediate **1d**. Retrocyanation leads to the product α-silyloxy ketone **3** and the metal cyanide needed to engage another equivalent of acylsilane, thus completing the catalytic cycle.

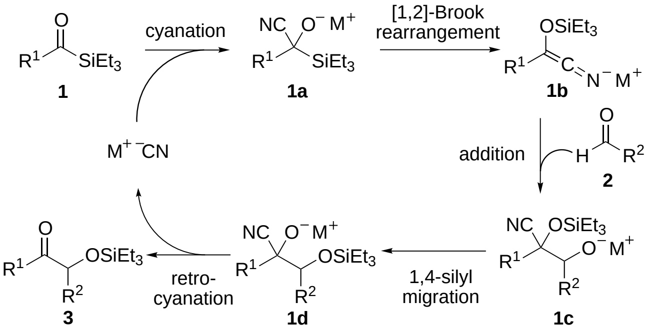
Having established a new direct method to form unsymmetrical α-silyloxy ketones, we wished to explore the possibility of effecting a second catalyzed construction of a carbon–carbon bond in the same pot (Scheme 3). Thus, benzoyl *tert*-butyldimethylsilane (**4**) and *p*-chlorobenzaldehyde (**5**) participated in a silyl benzoin addition catalyzed by KCN/[18]crown-6. Upon consumption of the acylsilane (TLC analysis), ethyl cyanoformate was added. The α-silyloxy ketone intermediate **6** underwent a sequential catalyzed cyanation, 1,4-silyl migration, and *O*-acylation with ethyl cyanoformate to afford silyl cyanohydrin carbonate **7** in 91 % yield as a single regioisomer (d.r. = 77:23, relative stereochemistry unassigned).[20] Conveniently, orthogonal protection of the product's two hydroxy groups is an inherent characteristic of the reaction. This result also demonstrates the utility of other silyl groups in the cross silyl benzoin addition.

In summary, cyanide-catalyzed silyl benzoin reactions have been developed to afford unsymmetrical silyl ether protected benzoin adducts with complete regiocontrol. A sequential silyl benzoin addition/cyanation–*O*-acylation reaction that resulted in two new C–C bonds was achieved in excellent yield. The operationally simple reaction proceeds at ambient temperature and provides a convenient method for direct introduction of the protected α-hydroxy ketone moiety. Asymmetric modification of both reactions is a current focus of research.

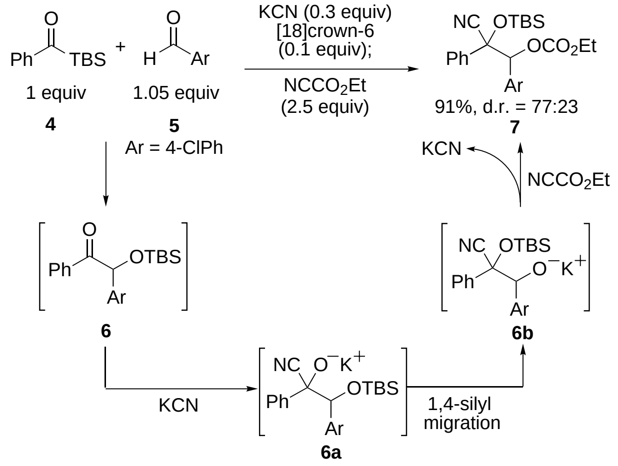
Table 1: (Continued)

Entry	R^1	R^2	Product	Yield [%][b]
15	Ph	*n*-hexyl	 3o	70
16	*n*-hexyl	Ph	 3p	51[d]

[a] R^{1}C(O)SiEt$_3$ (1.0 equiv), R^{2}CHO (1.1 equiv), [18]crown-6 (0.1 equiv), and KCN (0.3 equiv) in Et$_2$O at 25 °C for 1–5 h unless otherwise noted. See Supporting Information for details. [b] Yield of isolated analytically pure material. [c] Reaction time = 10 h. [d] R^{1}C(O)SiEt$_3$ (1.0 equiv), R^{2}CHO (4.0 equiv), [18]crown-6 (0.3 equiv), and KCN (0.5 equiv) in Et$_2$O at 25 °C.



Scheme 2. Proposed mechanism for the cross silyl benzoin addition reaction.



Scheme 3. Sequential one-pot silyl benzoin addition/cyanation–acylation reaction. TBS = *tert*-butyldimethylsilyl.

Experimental Section

Representative procedure: Synthesis of **3a**: A dry round-bottom flask with a magnetic stir bar was charged with acylsilane (104 mg, 0.47 mmol), KCN (8.0 mg, 0.12 mmol), [18]crown-6 (13 mg, 0.047 mmol), and Et$_2$O (8 mL). To the resulting mixture was added neat benzaldehyde (53 μL, 0.52 mmol) by syringe. The reaction mixture was stirred at 25 °C under N$_2$ until the starting material was consumed (2.5 h, TLC analysis). To the reaction mixture was added H$_2$O (15 mL). The mixture was stirred for 5 min before the organic layer was separated and the aqueous layer was extracted with Et$_2$O (3 × 15 mL). The organic extracts were combined and dried (MgSO$_4$), and the solvent was removed with a rotary evaporator. The product was purified by flash chromatography, eluting with 33:1 hexanes/EtOAc to afford **3a** as a clear oil (140 mg, 90 % yield). Analytical data for **3a**: ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.02$–8.00 (m, 2H), 7.53–7.51 (m, 2H), 7.46–7.42 (m, 1H), 7.35–7.30 (m, 4H), 7.25–7.21 (m, 1H), 5.77 (s, 1H), 0.88 (t, $J = 8.0$ Hz, 9H), 0.64–0.57 ppm (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): $\delta = 198.8$, 139.0, 134.5, 132.8, 129.8, 128.5, 128.1, 127.7, 125.8, 80.0, 6.6, 4.7 ppm; IR (thin film): $\tilde{\nu} = 3087$, 3062, 3029, 2957, 2913, 2877, 1700, 1680, 1598, 1579, 1493, 1448, 1413, 1277, 1238, 1190, 1119, 1071, 1004, 980, 850, 764, 745, 606 cm^{-1}; TLC (33:1 hexanes/EtOAc) $R_f = 0.17$; elemental analysis (%) calculated for C$_{20}$H$_{26}$O$_2$Si: C 73.57, H 8.03; found: C 73.22, H 8.05.

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Keywords: benzoin condensation · ketones · phase-transfer catalysis · rearrangements · umpolung

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