JOC Note

Cross Silyl Benzoin Additions Catalyzed by Lanthanum Tricyanide

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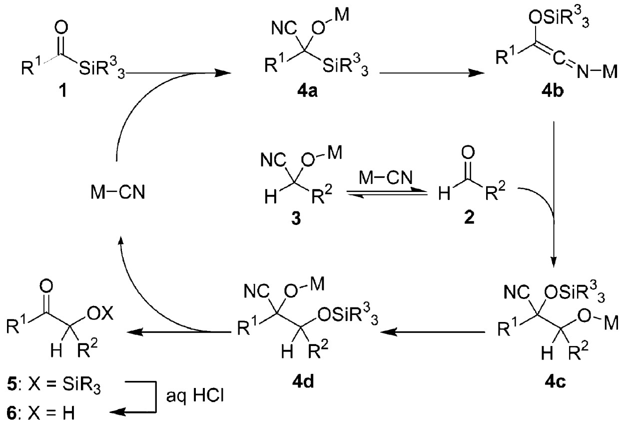
Abstract: From a screen of (cyanide)metal complexes, an improved catalyst for the cross silyl benzoin addition was discovered. Several $M(CN)_3$ complexes (M = Ce, Er, Sm, Y, Yb, La) were evaluated and lanthanum tricyanide was identified as the optimal catalyst. The catalyst, prepared in situ from $LaCl_3$, effects the selective coupling of aryl and alkyl acylsilanes with aryl, heteroaryl, α,*β*-unsaturated, and aliphatic aldehydes. The reactions occur at ambient temperature in less than 5 min to provide, depending on the workup, α-hydroxy or α-silyloxy ketones in 48−93% isolated yield.

The benzoin condensation[1−5] and its congeners[6−11] are important methods for the synthesis of α-hydroxy carbonyls. The reaction represents one of the most direct routes to such compounds, but lack of regiochemical control in the cross benzoin reaction of two different aldehydes can be a limitation. The benzoin condensation tends to be reversible, and as such, the product distribution for dimerization of two aldehydes is often determined by the relative thermodynamic stabilities of the four possible isomeric products.[1,4] The cross silyl benzoin reaction between acylsilanes and aldehydes has been reported as a kinetically controlled, regiospecific alternative to the traditional benzoin condensation.[12] The reaction relies on generation of an acyl anion equivalent via addition of CN to an acylsilane (**1** → **4a**) followed by [1,2]-Brook rearrangement[13−17] (**4a** → **4b**, Scheme 1).

The KCN/18-crown-6 catalyst system[12] performed well for aryl-aryl′ combinations (ArCOCH($OSiEt_3$)Ar′) but produced lower yields for alkyl-aryl′ products (R_{alkyl}-COCH($OSiEt_3$)Ar) and afforded <20% alkyl-alkyl′ adducts ($R_{alkyl}COCH(OSiEt_3)R'_{alkyl}$). The purpose of this paper is to document progress in the discovery of transition metal cyanide catalysts for the cross silyl benzoin reaction that provide enhanced reactivity for both aryl and aliphatic substrates; the described systems should provide a useful platform for the development of enantioselective catalysts.

SCHEME 1. Proposed Mechanism for Cross Silyl Benzoin Addition



An implicit requirement for successful catalysis of the cross silyl benzoin reaction is the ability of alkoxide **3** to undergo retrocyanation. If the cyanation of aldehyde **2** is irreversible, **3** becomes a nonproductive shunt of the M-CN catalyst and acylsilane cyanation (**1** → **4a**) is not possible. We initially considered the possibility that (salen)Al-CN complexes might be effective catalysts based on the recent observation that such species react with acylsilanes to produce (silyloxy)nitrile anions **4b** (M = Al(salen));[18] however, the absence of benzoin catalysis in a test reaction (Table 1, entry 1) hinted at the stability of tetrahedral intermediate **3** (M = Al(salen)). We evaluated (cyanide)lanthanum complexes[19] guided by the hypothesis that the derived alkoxide complexes **3** might tend to form reversibly. Attempts with lanthanum *i*-propoxides activated by Me_3SiCN failed to provide catalysts with reproducible activity (entries 2 and 3); however, $La(CN)_3$ generated from (n-Bu)$_3$La/Me_3SiCN[20] was found to be an effective catalyst that provided consistent yields. $LaCl_3$ (0.1 equiv) was treated with *n*-butyllithium (0.3 equiv), nominally yielding a tributyllanthanum species that upon subsequent addition of Me_3SiCN provided the active catalyst. Six different (cyanide)lanthanum catalysts were evaluated in the reaction between benzoyl dimethylphenylsilane (**1a**, prepared in one step from benzoyl chloride) and 4-chlorobenzaldehyde (**2a**); the results are listed in Table 1.

All catalysts were generated in situ, and the starting materials **1a** and **2a** were added to the catalyst suspen-

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[1] Ide, W. S.; Buck, J. S. *Org. React.* **1948**, *4*, 269−304.
[2] Lapworth, A. *J. Chem. Soc* **1903**, *83*, 995.
[3] Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699−702.
[4] Stetter, H.; Daembkes, G. *Synthesis* **1977**, 403−404.
[5] Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328.
[6] Rozwadowska, M. D. *Tetrahedron* **1985**, *41*, 3135−3140.
[7] Ricci, A.; Degl'Innocenti, A.; Chimichi, S.; Fiorenza, M.; Rossini, G. *J. Org. Chem.* **1985**, *50*, 130−133.
[8] Heck, R.; Henderson, A. P.; Kohler, B.; Retey, J.; Golding, B. T. *Eur. J. Org. Chem.* **2001**, 2623−2627.
[9] Pohl, M.; Lingen, B.; Müller, M. *Chem. Eur. J.* **2002**, *8*, 5288−5295.
[10] Cunico, R. F. *Tetrahedron Lett.* **2002**, *43*, 355−358.
[11] Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070−3071.
[12] Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534−2536.
[13] Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84.
[14] Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 2, 5609−5617.
[15] Degl'Innocenti, A.; Ricci, A.; Mordini, A.; Reginato, G.; Colotta, V. *Gazz. Chim. Ital.* **1987**, *117*, 645−648.
[16] Takeda, K.; Ohnishi, Y. *Tetrahedron Lett.* **2000**, *41*, 4169−4172.
[17] Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084.
[18] Nicewicz, D. A.; Yates, C. M.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2652−2655.
[19] Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004.
[20] Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209−6212.

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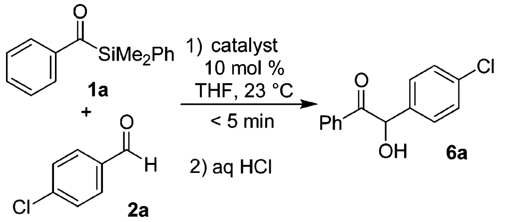
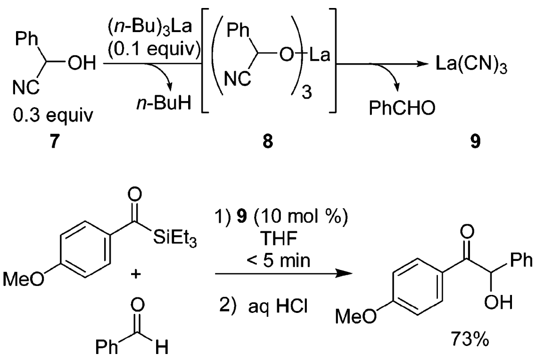
TABLE 1. Evaluation of M(CN)$_n$ Complexes as Cross Silyl Benzoin Catalysts



entry	catalyst	% yield[a]
1	(salen)Al-CN	0
2	Er(iOPr)$_3$/Me$_3$SiCN	42−66
3	Yb(iOPr)$_3$/Me$_3$SiCN	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. [b] Catalyst prepared via treatment of 0.1 equiv of (n-Bu)$_3$M with 0.3 equiv of Me$_3$SiCN (see text).

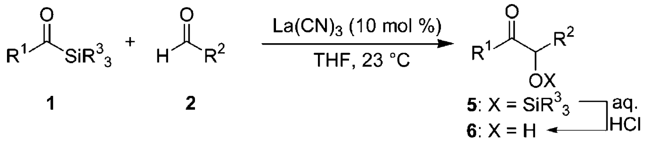
SCHEME 2. Test for Reversibility of Aldehyde Cyanation

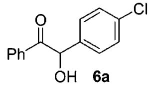
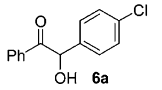
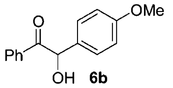
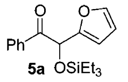
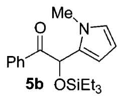
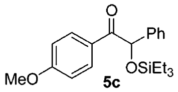
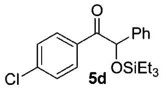
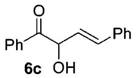
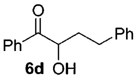
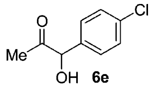
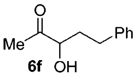


sion. Although all of the (cyanide)lanthanum complexes delivered the desired α-hydroxy ketone **6a** (after acidic workup), La(CN)$_3$ was the metal cyanide that afforded the highest yield (entry 6). Having identified the optimal (cyanide)metal catalyst, the scope of the cross benzoin reaction was further investigated (Table 2).

All reactions conducted with benzoyl trimethylsilane (**2b**) were subjected to subsequent silyl ether deprotection with aqueous HCl upon completion of the reaction. The reaction time for the KCN/18-crown-6 catalyzed cross silyl benzoin additions ranged from 1 to 5 h, whereas La(CN)$_3$ typically catalyzed the reactions in less than 5 min. The La(CN)$_3$ catalyst gave yields comparable to that of the KCN/18-crown-6 catalyst previously reported for aryl-aryl′ benzoin adducts (entries 1−3). 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). Compared with the KCN/18-crown-6 system, significant improvement has been observed for alkyl-aryl′ and alkyl-alkyl′ benzoin adducts. In the previous report, catalyst loading and electrophile concentration had to be significantly increased to achieve satisfactory yields. La(CN)$_3$ catalyzes the silyl benzoin reaction of acetyl trimethylsilane and 4-chlorobenzaldehyde in reasonable yield (entry 10), and for the first time that we are aware, cyanide catalysis has proven effective (albeit in intermediate yield) for the synthesis of alkyl-alkyl′ acyloins (entry 11). A large excess of aldehyde is not required in this case.[8]

TABLE 2. Catalyzed Silyl Benzoin Addition Reactions of Acylsilanes and Aldehydes[a]



entry	acylsilane	R^2	product	% yield[b]
1[c]	PhCOSiMe$_2$Ph	4-ClPh		75
2[c]	PhCOSiMe$_3$	4-ClPh		87
3[c]	PhCOSiMe$_3$	4-MeOPh		81
4	PhCOSiEt$_3$	2-furyl		88
5	PhCOSiEt$_3$	N-Me-2-pyrroyl		93
6	4-MeOPh-COSiEt$_3$	Ph		84
7	4-ClPh-COSiEt$_3$	Ph		83
8[c]	PhCOSiMe$_3$	(E)-CH=CHPh		50[d]
9[c]	PhCOSiMe$_3$	CH$_2$CH$_2$Ph		64[d]
10[c]	MeCOSiMe$_3$	4-ClPh		70[d]
11[c]	MeCOSiMe$_3$	CH$_2$CH$_2$Ph		48[d]

[a] R^{1}C(O)SiR$_3$ (1.0 equiv), R^{2}CHO (1.1 equiv), LaCN$_3$ (0.1 equiv) in THF at 25 °C for <5 min. 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^{1}C(O)SiMe$_3$ (1.0 equiv), R^{2}CHO (1.5 equiv), LaCN$_3$ (0.1 equiv) in THF at 25 °C for 15 min.

The reversibility of aldehyde cyanation in the present reactions was verified through the use of mandelonitrile (**7**) as a catalyst precursor in conjunction with (n-Bu)$_3$La (Scheme 2). Reaction of the (tributyl)lanthanum species with the cyanohydrin should be rapid and irreversible to generate tris(alkoxide) **8** (with concomitant generation of butane). If aldehyde cyanation is reversible (**8** → **9**), benzaldehyde extrusion should yield a competent catalyst. Thus, a solution of freshly prepared (n-Bu)$_3$La (0.1

equiv) was treated with a THF solution of PhCH(OH)-CN, followed by a THF solution of (p-MeOPh)COSiEt$_3$ and PhCHO. The cross benzoin product (p-MeOPh)-COCH(OH)Ph was obtained in 73% yield after acidic workup, consistent with our working hypothesis. It is interesting to note the contrast to the classic benzoin condensation, in which aldehyde cyanation is the crucial initiating step: in the present reactions no productive chemistry arises from M-CN addition to RCHO.

In summary, an improved catalyst for the cross silyl benzoin addition has been developed. A (cyanide)lanthanum complex is successful with a range of substrates and allows for simple, regiospecific synthesis of α-hydroxy ketones and their silyl-protected progenitors. The reaction proceeds rapidly at ambient temperature with a catalyst system that should provide a useful platform for the development of enantioselective variants. To this end, appropriate modifications of the (cyanide)metal complexes are currently under investigation and will be reported in due course.

Experimental Section

Preparation of LaCN$_3$ as a Solution in THF. A flame-dried 25-mL round-bottom flask with a magnetic stir bar was charged with 0.04 mmol of LaCl$_3$ and 3 mL of THF in a drybox. The flask was removed and cooled to −78 °C under a N$_2$ atmosphere. After 15 min, *n*-butyllithium (1.6 M in hexanes, 0.12 mmol, 3.0 equiv) was added via syringe. The resulting solution was stirred for 15 min at the same temperature before warming to 0 °C. After 30 min of stirring, 0.12 mmol of trimethylsilyl cyanide (3 equiv) was added, and the mixture was stirred for 30 min at the same temperature and then slowly warmed to room temperature.

2-(4-Chlorophenyl)-2-hydroxy-1-phenylethanone (6a). Typical Experimental Procedure. To a solution of La(CN)$_3$ was added via cannula a solution of benzoyl trimethylsilane (0.40 mmol, 1.0 equiv) and 4-chlorobenzaldehyde (0.44 mmol, 1.1 equiv) in 8 mL of THF. Upon completion of the reaction, 5 mL of 1 M HCl was added at 23 °C. After 30 min, 10 mL of Et$_2$O were added, and the organic layer was washed twice with 10 mL of H$_2$O. The aqueous layer was extracted with three 20-mL portions of Et$_2$O. The organic extracts were combined and dried with MgSO$_4$. The solvent was removed with a rotary evaporator. The residue was purified by flash chromatography, eluting with 20% EtOAc/hexanes to afford 74 mg (87%) of the known compound **6a** as a white solid:[21] ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.87 (d, $J = 7.5$ Hz, 2H), 7.52 (t, $J = 7.5$ Hz, 1H), 7.39 (t, $J = 7.5$ Hz, 2H), 7.29−7.25 (m, 4H), 5.92 (s, 1H), 4.57 (br s, 1H).

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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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[21] Heilmann, S. M.; Rasmussen, J. K.; Smith, H. K., II. *J. Org. Chem.* **1983**, *48*, 987−992.