

Lanthanum Tricyanide-Catalyzed Acyl
Silane–Ketone Benzoin Additions

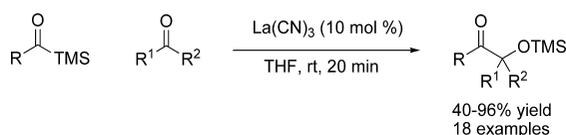
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ABSTRACT



Lanthanum tricyanide efficiently catalyzes a benzoin-type coupling between acyl silanes and ketones. Yields range from moderate to excellent over a broad substrate scope encompassing aryl, alkyl, electron-rich, and sterically hindered ketones.

α -Hydroxycarbonyls are valuable building blocks for numerous targets in organic synthesis.¹ The benzoin addition provides direct access to α -hydroxy ketones, and its strategic application has grown in the past decade. In addition to traditional metal cyanide catalysts,² N-heterocyclic carbenes and metallophosphites have been identified as efficient asymmetric catalysts for intramolecular and intermolecular benzoin reactions³ and the cross silyl benzoin reaction.⁴

Despite the wide range of electrophiles that have been successfully engaged by acyl anion equivalents in the benzoin and cross silyl benzoin reactions, the direct catalytic coupling of acyl anion equivalents to ketones remains a challenge due to the lower reactivity of ketones that presumably permits nonproductive enolization to become competitive. Stoichiometric methods for ketone acylation do exist; however, general strategies are not in place for conducting those reactions asymmetrically.⁵ Suzuki,^{6,3c} Enders,^{7,3d} and You⁸ have reported carbene-catalyzed intramolecular aldehyde–

ketone benzoin cyclization for the formation of five- and six-membered rings (Figure 1). Asymmetric variants for the

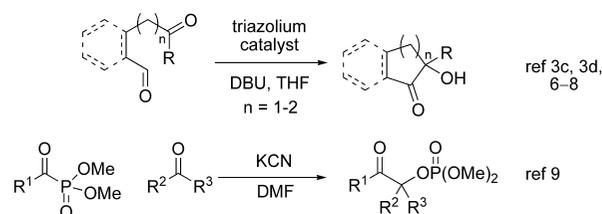


Figure 1. Previous examples of aldehyde–ketone benzoin reactions.

intramolecular reaction have also been reported that proceed in up to 98% yield and 99% ee.^{6b,7,8}

The single example of intermolecular catalytic ketone acylation comes from the recent work of Demir and co-workers,⁹ who described the cyanide-catalyzed coupling of acyl phosphonates¹⁰ with ketones in chemical yields of

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(4) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070–3071.

(5) Deprotonation of silyl cyanohydrins: (a) Bunnelle, E. M.; Smith, C. R.; Lee, S. K.; Singaram, S. W.; Rhodes, A. J.; Sarpong, R. *Tetrahedron* **2008**, *64*, 7008–7014. (b) Wessig, P.; Glombitza, C.; Mueller, G.; Teubner, J. *J. Org. Chem.* **2004**, *69*, 7582–7591. Lithiation of vinyl ethers: (c) Palomo, C.; Oiarbide, M.; Arceo, E.; Garcia, J. M.; Lopez, R.; Gonzalez, A.; Linden, A. *Angew. Chem., Int. Ed* **2005**, *44*, 6187–6190. Deprotonation of dithianes: (d) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joulle, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784–3793.

41–95%; however, the reaction is largely limited to electron-poor ketones. In general, enolizable protons were replaced with fluorine while *ortho*-substituted aryl and aryl-methyl ketones typically failed to give the desired product. Tuning of the reaction conditions and/or addition of a cocatalyst ($\text{Cu}(\text{OTf})_2$ or thiourea) was required for certain substrate combinations.

Our laboratory has developed the use of acyl silanes as acyl anion equivalents in the racemic¹¹ and enantioselective⁴ cross silyl benzoin reaction. Additionally, we have found $\text{La}(\text{CN})_3$ to be a particularly reactive catalyst for promoting the cross silyl benzoin between acyl silanes and aldehydes, with reaction times under 5 min.¹² We postulated that under $\text{La}(\text{CN})_3$ catalysis we might be able to engage ketone electrophiles with acyl silanes. We were hopeful that these conditions might lead to a more general reaction for intermolecular ketone acylation. Pitfalls to be navigated in this variant include undesired dimerization of the acyl silane, nonproductive proton transfer between the (silyloxy)nitrile anion intermediate and the ketone electrophile, and potential retro-benzoin reaction¹³ of the α -silyloxy ketone product (Figure 2).

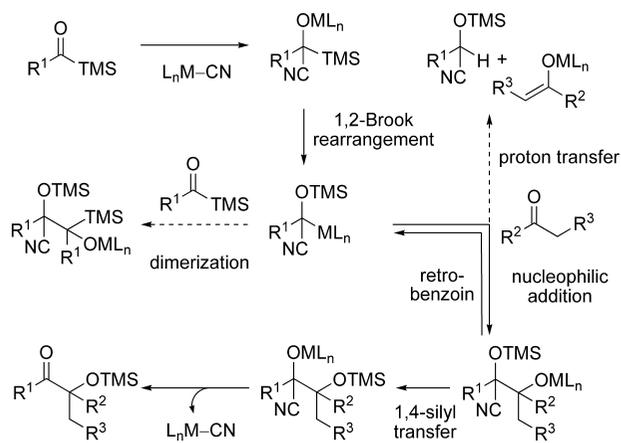


Figure 2. Proposed acyl silane–ketone benzoin reaction.

Gratifyingly, acyl silane **1a** reacted with 1 equiv of acetophenone in the presence of 20 mol % of $\text{La}(\text{CN})_3$ in

THF to deliver the desired α -hydroxyketone product in approximately 40% yield within 20 min. Competing with desired product formation was the deprotonation of acetophenone, leading to the quenched silyl cyanohydrin (**3**). In contrast to the aldehyde silyl benzoin reaction,¹¹ the ketone benzoin addition is apparently reversible: subsection of the product **2a** to the reaction conditions led to the formation of **3a** and acetophenone. For the reaction of **1a** with acetophenone, the retro-benzoin occurs at a much slower rate than the forward reaction and was minimized by shorter reaction times. Employing 2 equiv of ketone proved to be optimal, as a slight decrease in yield was observed when 3 equiv was used. We screened a number of metal cyanide catalysts and found that numerous $\text{M}(\text{CN})_n$ species effectively promoted the reaction and gave complete conversion (Table 1);

Table 1. Catalyst Screen and Optimization^a

entry	catalyst ^b	x mol %	convn (%) ^c	2a:3 ^d	yield (%) ^e
1	$\text{Ce}(\text{CN})_3$	20	100	3.2:1	nd
2	$\text{Y}(\text{CN})_3$	20	100	4.5:1	nd
3	$\text{Yb}(\text{CN})_3$	20	100	6.5:1	nd
4	$\text{Sc}(\text{CN})_3$	20	100	6.8:1	nd
5	$\text{Er}(\text{CN})_3$	20	100	8.0:1	nd
6	$\text{Hf}(\text{CN})_4$	20	100	8.6:1	nd
7	$\text{La}(\text{CN})_3$	20	100	10.5:1	nd
8	$\text{La}(\text{CN})_3$	10	100	nd	95
9	$\text{La}(\text{CN})_3$	5	100	nd	94
10	$\text{La}(\text{CN})_3$	2	62	nd	nd
11	$\text{La}(\text{CN})_3$	1	7	nd	nd

^a Conditions: 1.0 equiv of **1a**, 2.0 equiv of ketone, THF, $[\mathbf{1a}]_0 = 0.04$ M, rt, 20 min. ^b Catalyst prepared in situ as described in the Supporting Information. ^c Conversion determined by ¹H NMR spectroscopy. ^d Ratio of **2a**:**3** determined by ¹H NMR spectroscopy. ^e Yields of analytically pure material after SiO_2 column chromatography.

however, $\text{La}(\text{CN})_3$ provided the highest ratio of desired product to the quenched cyanohydrin.¹⁴ Optimization of the catalyst loading showed that the benzoin product could be obtained in up to 95% yield with 10 mol % catalyst loading. Lowering the catalyst loading to 5 mol % provided the product with no change to the conversion or yield. Upon further reduction of the catalyst loading to 2 mol % and 1 mol %, the reaction stalled with incomplete conversion after 24 h.

With optimized conditions in hand, we wished to examine the scope of the reaction. Using acyl silane **1a**, we varied the ketone employed (Table 2). The reactions proceeded with complete consumption of acyl silane, with isolated yields ranging from 40 to 95%. It should be noted that all examples

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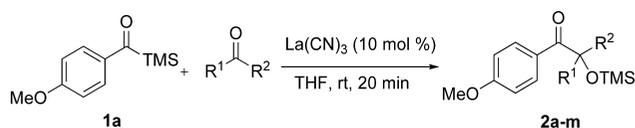
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Table 2. Scope of Ketone Coupling Partner^a

entry	product	structure	yield (%) ^b
1	2a		96
2	2b		92
3	2c		91
4	2d		85
5	2e		77
6 ^c	2f		61
7 ^c	2g		60
8	2h		73
9 ^c	2i		63
10	2j		86
11	2k		80
12 ^c	2l		85
13 ^c	2m		40

^a Conditions: 1.0 equiv of **1a**, 2.0 equiv of ketone, 0.10 equiv of La(CN)₃, THF, [**1a**]₀ = 0.04 M, rt, 20 min. ^b Yields of analytically pure material after SiO₂ column chromatography. ^c Product was treated with 1.0 equiv of TBAF at 0 °C for 10 min to enable purification. Yield reported over two steps.

employed enolizable electrophiles. The major byproduct in all cases was the quenched cyanohydrin, which accounts for

most of the remaining mass balance. For some substrates, it was convenient to deprotect the silyl ether to the alcohol using TBAF at 0 °C to separate the benzoin product from the ketone starting material. In all cases, the deprotection proceeded smoothly within 10 min, and elimination to the alkene was never observed.

As the feasibility of coupling sterically unhindered electron-deficient ketones had previously been demonstrated with acyl phosphonates, we focused our attention on expanding the scope of our reaction to include previously problematic substrates. Aromatic, heteroaromatic, and aliphatic ketones were well tolerated without any additional optimization of the reaction conditions or experimental procedure. The reaction also proved amenable to electron-neutral and electron-rich ketones. Ortho substitution was tolerated, although the yields were moderately lower. Entries 1, 8, and 9 demonstrate that the reaction is sensitive to the steric bulk of the alkyl substituent, with a decrease in yield observed moving from **2a** to **2h** to **2i**. Interestingly, cyclobutyl phenyl ketone allowed us to obtain **2i** in 60% yield, whereas isobutyrophenone (not shown) gave ~10% yield, despite a relatively small difference in the steric environments of each ketone. Unhindered aliphatic ketones were tolerated equally as well as aryl-alkyl ketones. Steric hindrance in 2-methylcyclohexanone led to a lower isolated yield of **2m**. Both **2l** and **2m** were isolated as single diastereomers. Ketones that failed to give appreciable coupling yields include isobutyrophenone, benzophenone, bicyclohexylketone, pinacolone, and methyl pyruvate (not shown).

In addition to varying the ketone component, we wished to examine the reaction's tolerance to the acyl silane coupling partner. The results of this survey are shown in Table 3. Electron-rich acyl silanes deliver a more nucleophilic (silyloxy)nitrile anion intermediate and performed the best, as expected.^{9,15} Yields of the coupling product decrease as a function of electron density on the aryl ring, as evidenced by entries 1, 3, and 4. The effect of steric hindrance in the acyl silane component was examined with entry 6, which delivered the desired product with a modest decrease in yield. In addition to aromatic acyl silanes, both heteroaromatic and aliphatic silanes were reasonably well tolerated. The more sterically demanding TES group was also tolerated with almost no decrease in yield (**4a**).

Products **2l** and **2m** demonstrate the stereoselectivity of the reaction with cyclic electrophiles, each being isolated as a single diastereomer. To determine the relative stereochemistry of the existing alkyl group and the newly introduced acyl group, 2-D NOESY was employed (Figure 3). In **2l**, an NOE was observed between the hydroxyl proton and the two axial γ -protons, as well as between the *ortho*-aryl protons and the axial β -protons on the cyclohexane ring. Similar NOE's were observed for

(14) The metallophosphite catalysts developed by our laboratory failed to successfully catalyze the reaction. See ref 4 and: Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem. Int. Ed* **2005**, *44*, 2377–2379.

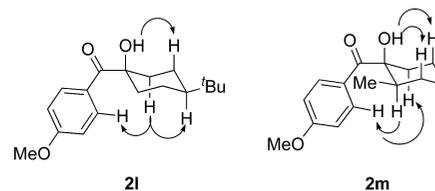
Table 3. Scope of Silane Coupling Partner^a

entry	product	structure	yield (%) ^b
1	2a		96
2	4a		93
3	4b		78
4 ^c	4c		62
5	4d		58
6	4e		81
7	4f		58

^a Conditions: 1.0 equiv of **1a**, 2.0 equiv of ketone, 0.10 equiv of La(CN)₃, THF, [**1a**]₀ = 0.04 M, rt, 20 min. ^b Yields of analytically pure material after SiO₂ column chromatography. ^c Product was treated with 1.0 equiv of TBAF at 0 °C for 10 min to enable purification. Yield reported over two steps.

compound **2m**. This leads us to propose the illustrated stereochemistry with the hydroxyl group *cis* to the existing

alkyl group, arising from an equatorial attack of the acyl silane to generate an axial alcohol.

**Figure 3.** NOESY analysis to determine equatorial attack.

In conclusion, we have developed a new intermolecular ketone acylation through a La(CN)₃-catalyzed silyl benzoin reaction employing acyl silanes as the acyl anion donor. The reaction works well for a number of aryl–alkyl and alkyl–alkyl ketones, greatly expands the scope of suitable ketones that can engage in benzoin-type reactions with acyl anion equivalents, and is operationally simple to perform. Efforts toward an asymmetric variant are underway.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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