Syntheses of Aldol Products and Cyanohydrins from Carboxylic Acids Using Hydrosilanes, Organosilicon Reagents, and Indium Triiodide Catalyst

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Carboxylic acids were applied to an indium triiodidecatalyzed reductive aldol reaction and a reductive cyanation in order to produce aldol adducts and cyanohydrins, respectively, in which the separate addition of two kinds of hydrosilanes was crucial in combination with either ketene silyl acetals or silyl cyanides.

Carboxylic acids are one of the most fundamental materials in organic synthesis.¹ Recent developments such as the Fukuyama reduction,² decarbonylative coupling,³ the Ugi reaction,⁴ the Arndt–Eistert synthesis,⁵ and catalytic reduction using hydrosilanes⁶ have increased the availability of carboxylic acids as starting materials. Sakai et al. also used hydrosilane to accomplish indium(III)-catalyzed reductive transformations from carboxylic acids to alkyl ethers,^{7,8} sulfides,⁹ and alkyl halides.¹⁰ However, only a few reports have described carbon– carbon bond formation at the carboxy moiety to furnish secondary alcohols, because the acidic proton often decomposes catalysts and carbon nucleophiles.¹¹

In this regard, we have recently developed the Friedel-Crafts acylation and cross-Claisen condensation using carboxylic acids by the combination of indium(III) catalyst and hydrosilane, where the in situ protection of a carboxylic moiety into a silyl ester by dehydrogenation is a key step.¹² In addition, a reductive aldol reaction using esters (Scheme 1, R = Me) has been developed, for which the combination of a ketene silvl acetal and HSiMe₂Ph is essential.¹³ These results prompted us to investigate a direct reductive aldol reaction using carboxylic acids. Unfortunately, this attempt furnished only 10% of the desired aldol product (Scheme 1, R = H), and a plausible reason would be the decomposition of a ketene silyl acetal by carboxylic acid. Herein, we wish to report a reductive aldol reaction using carboxylic acids, which was affected by the separate addition of two kinds of hydrosilanes, as shown in Scheme 2. This procedure is also possible using silvl cyanide instead of ketene silyl acetals.

Initially, two separate additions of HSiMe₂Ph were examined because it is the most suitable hydrosilane in the reaction of



Scheme 1. Reductive aldol recations using ester and carboxylic acid.

esters.¹³ After the treatment of carboxylic acid **1a**, HSiMe₂Ph, and indium triiodide catalyst for 3 min to form a silyl ester intermediate, the addition of ketene silyl acetal **2a** and HSiMe₂Ph resulted in unsatisfactory yield of the desired product **3aa** (Table 1, Entry 1).¹⁴ Next, various combinations of hydrosilanes (HSi¹ and HSi²) were investigated. When HSiEt₃ and H₃SiPh were used in the first and second steps, respectively, the

$$\begin{array}{c} O \\ R^{1} \underbrace{\bigcirc} OH + HSi^{1} \underbrace{\quad \text{cat. InI}_{3}}_{OH} \left[\begin{array}{c} O \\ R^{1} \underbrace{\bigcirc} OSi^{1} \end{array} \right] \underbrace{\quad \text{NuSiMe}_{3} + HSi^{2}}_{OR^{5}} \underbrace{\quad \text{HO} H}_{R^{1}} \underbrace{\quad \text{HO} H}_{R^{1}} \underbrace{\quad \text{Nu}}_{Nu} \\ \left(\begin{array}{c} \text{NuSiMe}_{3} = R^{3} \underbrace{\quad \text{OSiMe}_{3}}_{OR^{5}} , \text{ Me}_{3}\text{SiCN} \end{array} \right) \end{array}$$





		OSiMe ₃				
Ph 1a	O H <i>Si</i> cat. In OH rt, 3 m	$\begin{array}{c} 1 \\ X_3 \\ \text{inin} \end{array} \begin{array}{c} OMe \\ 2a \\ rt, 1 h \end{array}$				
	H Ph	O H O OMe ⁺ Ph 3aa 4	H H OH ⁺ Pr			OMe
Entry	HSi ¹	HSi ² (equiv)	InX ₃	Yield/% ^b		
				3aa	4 a	5aa
1	HSiMe ₂ Ph	HSiMe ₂ Ph (1.5)	InI ₃	44	4	24
2	HSiMe ₂ Ph	HSiEt ₃ (1.5)	InI ₃	24	0	3
3	HSiMe ₂ Ph	HSiMe ₂ Cl (1.5)	InI ₃	46	25	1
4	HSiMe ₂ Ph	HSi(OMe) ₃ (1.5)	InI ₃	16	0	13
5	HSiMe ₂ Ph	HSi(OEt) ₂ Me (1.5)	InI ₃	28	0	21
6	HSiMe ₂ Ph	TMDS (1.0)	InI ₃	64	5	3
7	HSiMe ₂ Ph	H ₃ SiPh (1.0)	InI ₃	77	1	4
8	HSiEt ₃	H ₃ SiPh (1.0)	InI ₃	87	1	0
9	PMHS ^c	H ₃ SiPh (1.0)	InI ₃	38	5	36
10	TMDS ^d	H ₃ SiPh (1.0)	InI ₃	34	2	35
11	H ₃ SiPh ^e	H ₃ SiPh (1.0)	InI ₃	3	15	33
12	HSiMe ₂ Cl	H ₃ SiPh (1.0)	InI ₃	2	35	7
13	HSi(OMe) ₃	H ₃ SiPh (1.0)	InI ₃	7	18	52
14	HSiEt ₃	TMDS (1.0)	InI ₃	70	5	4
15	HSiEt ₃	H ₃ SiPh (1.0)	InBr ₃	9	0	4
16	HSiEt ₃	H ₃ SiPh (1.0)	InCl ₃	0	0	0
17	HSiEt ₃	H ₃ SiPh (1.0)	In(OTf) ₃	0	0	0

^aReaction conditions: 1st step: **1a** (1 equiv), HSi^1 (1 equiv), catalyst (0.05 equiv), CH_2Cl_2 (1 M), rt, 3 min. 2nd step: **2a** (1.5 equiv), HSi^2 , rt, 1 h. ^bGC yields after work up. ^dTMDS (0.5 equiv) (TMDS: 1,1,3,3-tetramethylsiloxane). ^eH₃SiPh (0.33 equiv). ^ePMHS: polymethylhydrosiloxane.



Table 2. Scope of carboxylic acids 1 and ketene silyl acetals 2^a

^aReaction conditions: 1st step: **1** (1 equiv), HSiEt₃ (1 equiv), InI₃ (0.05 equiv), CH₂Cl₂ (1 M), rt, 3 min. 2nd step: **2** (1.5 equiv), H₃SiPh (1 equiv), rt, 1 h. Yields were determined by ¹HNMR analysis using an internal standard for crude products. Yields in parenthesis indicate side products **4**. ^bIn the 2nd step, **2** (2 equiv), H₃SiPh (2 equiv), rt, 2 h. ^cthreo/ erythro = 84:16. ^ddr = 62:38.

yield of **3aa** was increased to 87% along with a negligible amount of side product **4a** (Entry 8). It is noteworthy that no formation of cross-Claisen condensation product **5aa** was observed. In contrast, the formation of **5aa** was observed when using PMHS, TMDS, H₃SiPh, and HSi(OMe)₃ as HSi^1 because of the presence of the coordinating group on the siloxy moiety of the silyl ester intermediate (Entries 9–13).^{12b} The combinations of HSiMe₂Ph/TMDS, HSiMe₂Ph/H₃SiPh, and HSiEt₃/TMDS also gave good yields of the desired product **3aa** (Entries 6, 7, and 14). The effect of InI₃ was characteristic, and other indium compounds such as InBr₃, InCl₃, and In(OTf)₃ hardly promoted the reaction despite the higher Lewis acidity (Entries 8 and 15–17).¹⁵

With the optimized conditions in hand (Table 1, Entry 8), the scope of carboxylic acids 1 and ketene silyl acetals 2 was investigated (Table 2). Simple aliphatic carboxylic acids 1b and 1c gave high yields of the desired products 3ba and 3ca, respectively. Furthermore, several functional groups, chloro, bromo, alkenyl, and alkynyl, were compatible with the reaction conditions (3da, 3ea, 3fa, and 3ga). Cyclohexanecarboxylic acid (1h) also gave the corresponding alcohol 3ha in an 89% yield. However, the reaction of benzoic acid (1i) resulted in a low yield of 3ia because of further reduction of the benzylic hydroxy moiety.¹⁶ Carboxylic acid 1j possessed a chiral center at the α -position and afforded the product 3ja with a reasonable stereoselectivity. Disubstituted and monosubstituted ketene silyl acetals (2b, 2c, and 2d) also provided the desired products 3kb,





^aReaction conditions: 1st step: **1** (1 equiv), HSiEt₃ (1 equiv), InI₃ (0.05 equiv), CH₂Cl₂ (1 M), rt, 3 min. 2nd step: **6** (2 equiv), TMDS (1 equiv), rt, 1 h. Yields were determined by ¹HNMR analysis using an internal standard for crude products. Yields in parenthesis indicate side products **4**. ^bIn the 2nd step, the reaction was carried out for 2 h.

3ac, and **3ad** in moderate-to-high yields. Unfortunately, nonsubstituted ketene silyl acetals were not applicable to this reaction system because they are unstable under these conditions.

Silyl cyanide **6** was also found to be applicable to this reaction instead of ketene silyl acetal **2** (Table 3). In this case, the employment of TMDS in the second step successfully gave reductive cyanation product **7a** in 88% yield with a small amount of alcohol **4a**, and with no further reduction of the cyano moiety.¹⁷ Alkenyl and benzyloxy groups were tolerated under the reaction conditions to afford the corresponding cyanohydrins **7l** and **7m**, respectively. Cyclohexanecarboxylic acid (**1h**) also provided cyanohydrin **7h** along with 12% of side-product **4**. The transformation of pivalic acid (**1n**) to the corresponding cyanohydrin **7n** progressed despite the large steric hindrance.

Figure 1 shows a plausible reaction mechanism. The InI₃ catalyst apparently affects the dehydrogenation of carboxylic acid 1 with HSiEt₃ to provide silyl ester 8, because no reaction takes place without the catalyst.^{12b} In the second step, the InI₃catalyzed hydrosilylation of 8 with HSi² such as H₃SiPh and TMDS produces acetal intermediate 9. The employment of reactive HSi^2 was essential because in situ generated silvl ester 8 has a bulky alkoxy moiety (OSiEt₃) as compared to the ester.^{13a} Elimination of the siloxy moiety from 9 gives either the oxocarbenium ion 10 or aldehyde 11. Then, the nucleophilic addition of NuSiMe₃ 2 (or 6) affords silvl ether 12 and regenerates InI₃. When a mixture of 1a, 1 equiv of HSiEt₃, and ketene silvl acetal 2a was treated, a cross-Claisen condensation proceeded sluggishly, furnishing **5aa** in only 13% yield.¹⁸ This result strongly suggested that the hydrosilylation of silvl ester 8 by a powerful HSi² such as H₃SiPh and TMDS is essential in the second step. In contrast, mild hydrosilanes such as HSiEt₃ and HSiMe₂Ph are appropriate in the first step.

In summary, we have demonstrated the indium triiodidecatalyzed transformation of carboxylic acids to β -hydroxy esters and cyanohydrins. The separate addition of two kinds of hydrosilanes was an essential procedure, in which the generation of silyl ester intermediates between the carboxylic acid and a mild hydrosilane was followed by the addition of a powerful first step: dehydrogenation

$$\begin{array}{c} O \\ R^1 \\ OH \end{array} + HSiEt_3 \xrightarrow{\text{cat. Inl}_3} O \\ R^1 \\ H \\ OSiEt_3 \end{array} + H_2$$

second step: hydrosililation and functionalization



Figure 1. Reaction mechanism.

hydrosilane with ketene silyl acetals or silyl cyanide. A variety of functional components such as chloro, bromo, alkenyl, and alkynyl groups were compatible with this system.

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- 18 See the Supporting Information in the details of the experiments for the reactions of 1a, HSiEt₃, and NuSiMe₃ 2 (or 6) in the absence of HSi².¹⁹
- 19 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/ index.html.