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Synthetic Methods

# Indium Tribromide Catalyzed Cross-Claisen Condensation between Carboxylic Acids and Ketene Silyl Acetals Using Alkoxyhydrosilanes[**]

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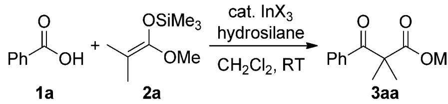
Carbon acylations play an important role in the construction of carbon frameworks having a carbonyl group. Among them, the Claisen condensation is one of the most useful methods, as it furnishes various β-ketoesters.[1] A classical example is the homocondensation of esters promoted by a strong base.[2] Recent successful developments in the cross-condensation between metal enolates and active acylating reagents, such as acid anhydrides or acid chlorides, have resulted in a reduction in side reactions.[3–5] Carboxylic acids are promising candidates as acylating reagents, but their direct use remains a challenging problem because the acidic proton often causes decomposition of the catalyst and undesired side reactions. Most of the reported reactions require the use of harsh reagents such as $SOCl_2$[6] or *N*,*N*′-carbonyldiimidazole to prepare active intermediates from carboxylic acids,[7] and these reactions result in troublesome by-products being generated. Recently, Tanabe and co-workers reported the cross-condensation of titanium and silyl enolates under mild reaction conditions, but the system also required an extra step to prepare active intermediates.[3c,4c] Herein, we describe a convenient indium-catalyzed cross-Claisen condensation, in which the simple and sequential addition of a carboxylic acid, an alkoxyhydrosilane, and a ketene silyl acetal in the presence of $InBr_3$ gives the desired product.

Owing to its moderate Lewis acidity, high tolerance to an acidic proton, and compatibility with various functional groups, we recently focused on using indium trihalides to achieve a direct coupling reaction of alcohols with various nucleophiles and the Friedel–Crafts acylation using carboxylic acids.[8,9] These results prompted us to attempt the condensation reaction between benzoic acid **1a** and dimethylketene methyltrimethylsilyl acetal (**2a**) in the presence of an indium trihalide. The use of a catalytic amount of $InBr_3$ gave hardly any condensation product (Table 1, entry 1) and the addition of $Me_3SiCl$ was ineffective (Table 1, entry 2). Next, the use of $Me_2ClSiH$, which was effective in the Friedel–Crafts acylation using carboxylic acids, furnished the desired product **3aa**, but the yield was only 39% despite a high reaction conversion (Table 1, entry 3).[9] These results indicated that the combination of an indium halide and a silyl halide, which often acts as a strong Lewis acid,[8d,e,10] is not applicable for this reaction. Gratifyingly, the employment of alkoxyhydrosilanes, instead of $Me_2ClSiH$, accelerated the cross-Claisen condensation, which was accompanied by the vigorous generation of hydrogen gas; $(MeO)_3SiH$ gave the best result (Table 1, entries 4–6).[11] This method has a clear advantage that the successive addition of all the reagents in the order of $InBr_3$, **1a**, hydrosilane, and **2a** gave high yields of **3aa**, and a specific step for the generation of an active acylating reagent was not required. When $Et_3SiH$ was used a rapid evolution of hydrogen gas occurred, but the desired product was obtained in only 7% yield (Table 1, entry 7). The use of $(MeO)_3SiH$ in the absence of indium trihalide furnished no product (Table 1, entry 8). The combination of $(MeO)_3SiH$ with $InI_3$ gave a satisfying result (Table 1, entry 9), while $InCl_3$ and $In(OTf)_3$ showed low activity (Table 1, entries 10 and 11).

*Table 1:* Cross-Claisen condensation between benzoic acid (**1a**) with dimethylketene silyl acetal **2a**.[a]



| Entry | $InX_3$ | Additive | Conversion of **1a** [%][b] | Yield of **3aa** [%][b] |
|---|---|---|---|---|
| 1 | $InBr_3$ | – | 7 | 3 |
| 2 | $InBr_3$ | $Me_3SiCl$ | 9 | 2 |
| 3 | $InBr_3$ | $Me_2ClSiH$ | 62 | 39 |
| 4 | $InBr_3$ | $(MeO)_3SiH$ | 100 | 90 |
| 5 | $InBr_3$ | $(EtO)_3SiH$ | 85 | 85 |
| 6 | $InBr_3$ | $(EtO)Me_2SiH$ | 80 | 80 |
| 7 | $InBr_3$ | $Et_3SiH$ | 14 | 7 |
| 8 | – | $(MeO)_3SiH$ | 7 | 0 |
| 9 | $InI_3$ | $(MeO)_3SiH$ | 86 | 72 |
| 10 | $InCl_3$ | $(MeO)_3SiH$ | 30 | 10 |
| 11 | $In(OTf)_3$ | $(MeO)_3SiH$ | 18 | 0 |

[a] **1a** (1 mmol), **2a** (2 mmol), $InX_3$ (0.1 mmol), additive (1.05 mmol), $CH_2Cl_2$ (1 mL), RT, 3 h. [b] Values were determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. Tf = trifluoromethanesulfonyl.

Direct acylations using a variety of carboxylic acids were examined under the optimized reaction conditions, which included $InBr_3$ catalyst, and $(MeO)_3SiH$ (Table 2). Aromatic carboxylic acids bearing either electron-donating and electron-withdrawing groups reacted with ketene silyl acetals **2a** to give the desired β-ketoesters **3** (Table 2, entries 1–3). Aliphatic carboxylic acids were also applicable except for the bulky pivalic acid (**1g**; Table 2, entries 4–6). A notable

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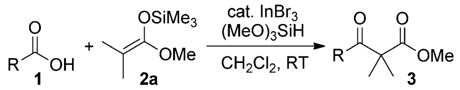
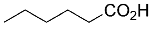
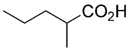
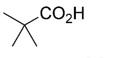
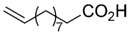
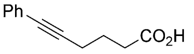
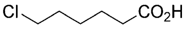
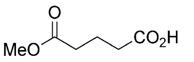
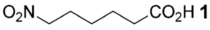
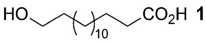
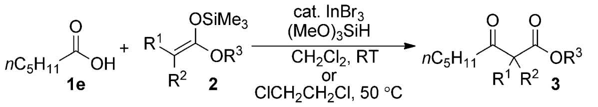
*Table 2:* Cross-Claisen condensation with various carboxylic acids.[a]

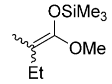
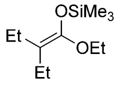
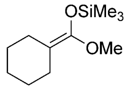
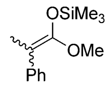
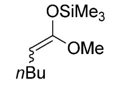
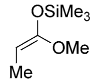


| Entry | 1 | 3 | Yield [%][e] |
|---|---|---|---|
| 1 | 4-$MeOC_6H_4CO_2H$ **1b** | **3ba** | 99 |
| 2 | 4-$MeC_6H_4CO_2H$ **1c** | **3ca** | 91 |
| 3 | 4-$ClC_6H_4CO_2H$ **1d** | **3da** | 67 |
| 4 |  **1e** | **3ea** | 93 |
| 5[b] |  **1f** | **3fa** | 53 |
| 6[b] |  **1g** | **3ga** | 0 |
| 7 |  **1h** | **3ha** | 86 |
| 8 |  **1i** | **3ia** | 56 |
| 9 |  **1j** | **3ja** | 85 |
| 10[c] |  **1k** | **3ka** | 50 |
| 11[b] |  **1l** | **3la** | 53 |
| 12[d] |  **1m** | **3ma** | 57 |

[a] **1** (1 mmol), **2a** (2 mmol), $InBr_3$ (0.1 mmol), $(MeO)_3SiH$ (1.05 mmol), $CH_2Cl_2$ (1 mL), RT, 3 h. [b] $ClCH_2CH_2Cl$ (1 mL), 50°C. [c] **2a** (1.2 mmol). [d] Stepwise addition: **1** (1 mmol), $InI_3$ (0.1 mmol) and $(MeO)_3SiH$ (1.2 mmol) were stirred at 50°C, then **2a** (2 mmol) and $Me_3SiCl$ (0.2 mmol) were added at RT and the reaction mixture was stirred for 3 h. [e] Yields were determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

*Table 3:* Cross-Claisen condensation between hexanoic acid (**1e**) and various types of ketene silyl acetals.[a]



| Entry | 2 | Conditions | 3 | Yield [%][b] |
|---|---|---|---|---|
| 1 |  **2b** | 50°C, 11 h | **3eb** | 99 |
| 2 |  **2c** | 50°C, 13 h | **3ec** | 99 |
| 3 |  **2d** | RT, 3 h | **3ed** | 99 |
| 4 |  **2e** | 50°C, 21 h | **3ee** | 29 |
| 5 |  **2f** | RT, 3 h | **3ef** | 51 |
| 6 |  **2g** | RT, 3 h | **3eg** | 45 |

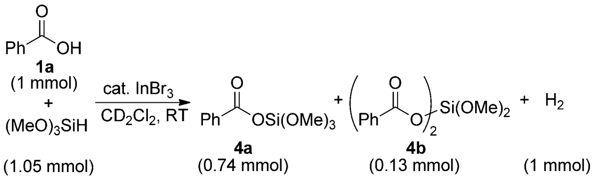
[a] **1e** (1 mmol), **2** (2 mmol), $InBr_3$ (0.1 mmol), $(MeO)_3SiH$ (1.05 mmol), solvent (1 mL). [b] Yields were determined by $^1H$ NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

advantage of this system is that alkenyl, alkynyl, chloro, nitro, and ester groups survived the reduction by the hydrosilane, perhaps because active metal hydrides are often needed to reduce these functional groups (Table 2, entries 7–11). Even the condensation with hydroxycarboxylic acid took place chemoselectively, although stepwise treatment and the addition of trimethylsilyl chloride were required (Table 2, entry 12).

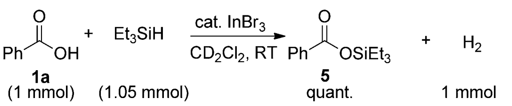
An investigation into the ketene silyl acetals that can be used in this reaction is summarized in Table 3. Dialkylketene silyl acetals **2b**–**2d** gave the corresponding β-ketoesters in excellent yields (Table 3, entries 1–3). The use of alkylarylketene silyl acetal **2e** resulted in a low yield because conjugation with the phenyl group decreased the nucleophilicity (Table 3, entry 4). The reactions of monosubstituted ketene silyl acetals **2f** and **2g** led to moderate yields (Table 3, entries 5 and 6). Unfortunately, it is a limitation at this stage that no desired product was obtained when using an unsubstituted ketene silyl acetal. Tables 2 and 3 demonstrate that a wide variety of carboxylic acids and ketene silyl acetals can be used in this reaction system.

To investigate the reaction mechanism, benzoic acid (**1a**) was treated with trimethoxysilane and triethylsilane in the presence of $InBr_3$ [Eqs. (1) and (2)]. In both cases, hydrogen gas was evolved in quantitative yields within 5 minutes.[12] In the case of trimethoxysilane, the formation of silyl benzoates **4a** and **4b** was observed by $^1H$ NMR spectroscopy in 0.74 mmol and 0.13 mmol, respectively.[13] Triethylsilane gave the corresponding silyl benzoate **5** quantitatively. The evolution of hydrogen gas was apparently promoted by $InBr_3$ because no reaction occurred in the absence of $InBr_3$. Next, it was found that, when using $InBr_3$ as the catalyst, isolated **4a** reacted with ketene silyl acetal **2a** to give the desired product **3aa** in 93% yield (Scheme 1). Although **4b** could not be isolated, both **4a** and **4b** were consumed to give **3aa** when the reaction mixture obtained in Equation 1 was directly treated with **2a**.[14] In contrast, the reaction using **5** resulted in only 5% yield of **3aa**. These results strongly suggest that silyl carboxylates bearing an alkoxy moiety, such as **4a** and **4b**, are key intermediates and that $InBr_3$ catalyzes both the intermediate-generation step and the subsequent reaction with silyl enolates.

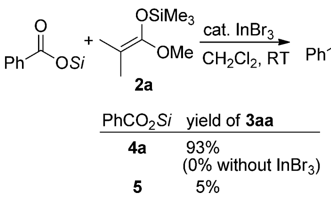
A tentative reaction mechanism is illustrated in Scheme 2. $(MeO)_3SiH$ abstracts the proton from the $InBr_3$-activated carboxylic acid **6** to generate a silyl carboxylate **4**, such as **4a** and **4b**, accompanied by the evolution of hydrogen gas. Then, ketene silyl acetal **2** reacts with the $InBr_3$-activated silyl



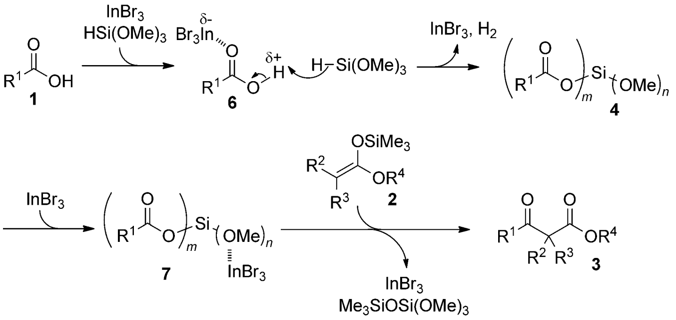
(1)



(2)



***Scheme 1.*** Cross-Claisen condensation using silyl carboxylate.



***Scheme 2.*** A tentative reaction scheme.

carboxylate **7** to give the Claisen-condensation product **3**; in this step the interaction between the oxygen atom of the methoxy group and $InBr_3$ may play an important role because the presence of the alkoxy moiety on a hydrosilane is essential.

In conclusion, the $InBr_3$-catalyzed cross-Claisen condensation between carboxylic acids and silyl ketene acetals was accomplished by using alkoxyhydrosilanes. The alkoxy moiety on the silicon center plays an important role to promote the condensation. This reaction was compatible with a diverse range of functional groups, including alkenes, alkynes, chlorides, alcohols, esters, and nitro groups. Further detailed studies of the reaction mechanism are in progress.

## *Experimental Section*

Typical procedure for the cross-Claisen condensation using benzoic acid (**1a**), dimethylketene methyltrimethylsilyl acetal (**2a**), and $(MeO)_3SiH$ (Table 1, entry 4): $(MeO)_3SiH$ (1.05 mmol) and **2a** (2 mmol) were added to a suspension of $InBr_3$ (0.1 mmol) and **1a** (1 mmol) in dichloromethane (1 mL). The reaction mixture was stirred for 3 h at room temperature and then was quenched by 1M aq HCl (5 mL). The resulting mixture was extracted with $Et_2O$. The organic layer was dried over $MgSO_4$, and the volatiles were removed under reduced pressure to afford the crude product, which was analyzed by $^1H$ NMR spectroscopy.

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**Keywords:** carboxylic acids · Claisen condensation · indium · ketene silyl acetals · silanes

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[11] The evolution of hydrogen gas was monitored for each of the hydrosilanes: 0.8 mmol for $(MeO)_3SiH$, 1 mmol for $Et_3SiH$, and 0.35 mmol for $Me_2ClSiH$.

[12] Details of the monitoring of the hydrogen generation is given in the Supporting Information.

[13] Ligand exchange between two molecules of silyl benzoate **4a** may give silyl benzoate **4b** and tetramethoxysilane, because tetramethoxysilane was observed by $^1H$ NMR spectroscopy in the reaction shown in Equation 1.

[14] Although silyl carboxylate **4b** could not be isolated, the reaction mixture obtained in Equation 1 was analyzed by NMR spectroscopy and MS to identify **4b**. Details of the reaction are included in the Supporting Information.