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Chemoselective allylic addition of allyltrichlorosilane to α-oxocarboxylic acids: synthesis of tertiary α-hydroxy carboxylic acids

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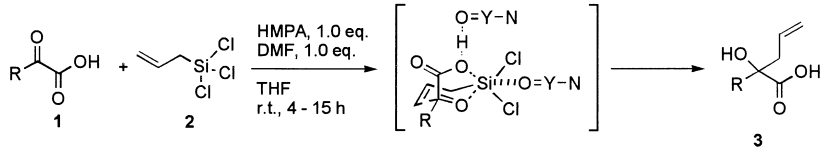
Abstract

Allyltrichlorosilane can add to α-oxocarboxylic acids in the presence of DMF and HMPA. The α-carboxylic substituent exerts a remarkable neighboring group effect on the reaction. The reaction presumably proceeds in an intramolecular fashion through a 'rigid' bicyclic transition state assembly involving a hypervalent silicate species, which produces the chemoselectivity approaching 100%. © 2000 Dupont Pharmaceuticals Company. Published by Elsevier Science Ltd. All rights reserved.

Tertiary α-hydroxy carboxylic acids are fairly common structural units in complex natural products, such as integerrimine,[1] monocrotaline[2] and methynolide.[3] Considerable efforts in this area have resulted in several synthetic methods for the synthesis of tertiary α-hydroxy carboxylic derivatives, for example, dihydroxylation of α,β-unsaturated esters[4] and enolate addition to α-keto esters.[5] However, few methodologies have been reported for the direct synthesis of tertiary α-hydroxy carboxylic acids. Previously, we have described our studies of allylboration of α-oxocarboxylic acids for the direct construction of tertiary α-hydroxy carboxylic acids.[6] The main advantage of this strategy is the ease of controlling the newly formed carbon–carbon bond through a favorable bicyclic transition state.



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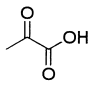
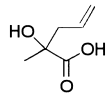
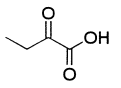
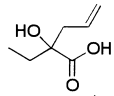
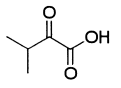
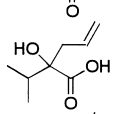
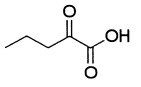
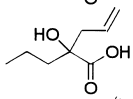
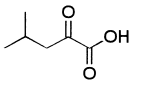
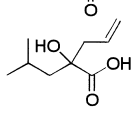
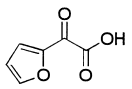
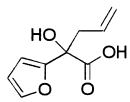
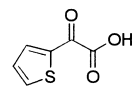
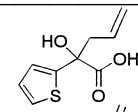
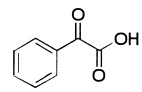
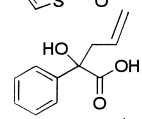
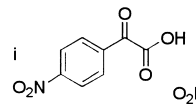
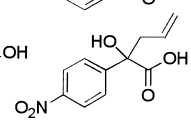
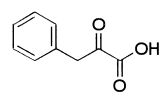
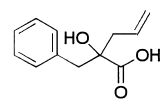
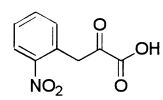
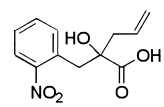
The addition of various allylmetal reagents to carbonyl compounds is one of the highly favorable methods for carbon–carbon bond formation. Among many allylic metallo systems studied thus far, borane or boronate, silane, stannane and indium have emerged as the most useful systems.[7] Whereas the allylboration of carbonyl compounds proceeds through a favorable chairlike transition state, the common allylsilation (employing allyltrimethylsilane) of carbonyl compounds takes place via an acyclic transition state in the presence of stoichiometric amounts of strong Lewis acids for the activation of the carbonyl partner.[7] By increasing the Lewis acidity by replacing the alkyl substituents on Si by electron-withdrawing groups, for example by fluoride or chloride, one can increase the reactivity of silane reagents, and consequently can increase the stereo- and regioselectivities of the allylsilation reactions.[7] Over the past few years, studies of the allylsilation of aldehydes using allyltrihalosilanes as reagents have appeared frequently; however, the allylic addition of allyltrihalosilanes to ketones has been very limited.[7] Interestingly, Sakurai reported that α-hydroxy ketones react with allyltrifluorosilane in the presence of triethylamine to afford tertiary α-1,2-diols in high diastereoselectivity via a bicyclic transition state.[8] Herein, we wish to report the allylsilation of α-oxocarboxylic acids (**1**) by commercially available allyltrichlorosilane (**2**) to produce tertiary α-hydroxy carboxylic acid (**3**), as shown in Eq. (1).

Initially, this reaction was conducted utilizing **2** to react with **1** in the presence of triethylamine in dichloromethane. In contrast to our previous observations[6] and to Sakurai's communication,[8] this reaction condition affords a very low yield of the corresponding adduct and a long period of reaction time. We then turned our attention to evaluate other Lewis bases to catalyze this reaction. Recently, Kobayashi[9] and Denmark[10] revealed that DMF or HMPA coordinates to the silicon atom of **2** to form a hypervalent silicate, which in turn reacts with aldehydes via a cyclic chairlike transition state to afford the corresponding homoallylic alcohol in a regio- and diastereoselective manner. Applying HMPA and/or DMF as Lewis bases in our study, we found that either DMF or HMPA can catalyze the addition reaction. However, the optimized condition involves the use of a combination of 1.0 equivalent of DMF and HMPA, respectively, to catalyze the addition reaction of **2** with **1**. In our case, it is necessary to have an extra equivalent of Lewis base to complex with the proton from the carboxylic acid group to drive the reaction to completion. Under these reaction conditions, the allyltrichlorosilane reagent **2** can easily add to both aliphatic and aromatic substrates in 3 to 16 h at room temperature in high yield (Table 1). Stoichiometric studies using benzoylformic acid as substrate revealed that 1.2 equivalents of **2** is sufficient enough to complete the reaction; however, it takes 9 h in propionitrile and 15 h in THF. On the other hand, when 2.0 equivalents of allyltrichlorosilane are employed, reactions can be completed in less than 4–5 h in either propionitrile or in THF. The solvent studies revealed that the preference of the solvent for the addition reaction is in the order of $CH_3CH_2CN{=}CH_3CN > THF \gg CH_2Cl_2$. For example, under the standard conditions (1.0 equivalent of HMPA and 1.0 equivalent of DMF as catalysts, 2.0 equivalents of **2** at room temperature) the allylic addition of benzoylformic acid takes 3–4 h in CH_3CH_2CN or in CH_3CN, 4–5 h in THF and 10–12 h in CH_2Cl_2 for the completion of the reaction.

In contrast to the allylation of α-oxocarboxylic acids (**1**) by **2**, which proceeds rapidly and smoothly in the presence of HMPA and DMF at room temperature to yield the desired tertiary α-hydroxy carboxylic acids (**3**) chemoselectively, the corresponding allylation of α-oxocarboxylic ester or ketone under the same conditions reacts very slowly. For example, the reaction of **2** with benzoylformic methyl ester in the presence of DMF/HMPA requires 60 h at room temperature for complete conversion; and methyl benzylphenone does not react with **2** under the same conditions. The selectivity and the enhanced reactivity of the α-oxocarboxylic acids suggest that

Table 1
Synthesis of *tert*-α-hydroxy carboxylic acids[a]

	Oxocarboxylic Acid, **1**	Product[b] **3**	Reaction Time (h)	Yield (%)[c]
a			3	60
b			4	74
c			15	73
d			5	89
e			5	88
f			5	92
g			5	96
h			4	91
i			4	89
j			6	59
k			6	54

[a] Reactions were run in THF employing 2.0 eq. of allyltrichlorosilane at r.t. in the presence of 1.0 eq. of HMPA and DMF, respectively. [b] Structures are determined by ^{1}H, ^{13}C-NMR and MS Spectra. [c] Isolated yield.

the reaction proceeds via a 1,3-bridged cyclohexane-like transition state. Thus, the α-carboxylic group not only activates the neighboring keto group, but also participates in the allylation reaction through complexation with the silicon atom, which in turn complexes with the keto group to form a bicyclic transition state assembly with a hypervalent silicate species as shown in Eq. (1).

The proposed transition state assembly is consistent with the increased reactivity of the carboxylic acid compared to the esters as well as the rate enhancement with at least 2 equivalents of DMF and/or HMPA. Our results are summarized in Table 1. Typically, α-oxocarboxylic acids (**1**) are treated with HMPA and DMF (1.0 equivalent, respectively), at room temperature for 2 min, and then with allyltrichlorosilane (**2**, 2.0 equivalents) at room temperature for 4–16 h. Upon completion of the reaction, the reaction mixture is quenched with water. After basic hydrolysis and acidic workup, the desired α-tertiary hydroxy carboxylic acids **3** are obtained in 54–96% yield (Table 1).

In summary, we have demonstrated that the α-oxocarboxylic functionality exerts a remarkable neighboring group effect on the allylic addition reaction of allyltrichlorosilane to α-oxocarboxylic acid to form the corresponding tertiary α-hydroxy carboxylic acid employing DMF and HMPA as catalysts. The reaction presumably proceeds through a 'rigid' bicyclic transition state assembly involving 'hypervalent' silicate species. The asymmetric version of this reaction is currently under investigation.[11]

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11. The synthesis of (±)-2-hydroxyl-2-(2-thienyl)-4-pentenoic acid (3 g) is representative: To a stirred solution of 2-thiopheneglyoxylic acid (0.78 g, 5.0 mmol) in anhydrous THF (6.0 ml) at 20°C containing HMPA (0.90 g, 5.0 mmol) and DMF (0.37 g, 5.0 mmol) was added allyltrichlorosilane (1.75 g, 10.0 mmol), dropwise. The reaction mixture was stirred for 4–6 h at room temperature; and then quenched by the slow addition of water (10.0 ml) at 0°C, and basified to pH >12.0 with aqueous 5.0N NaOH. The mixture was washed with *tert*-butylmethyl ether. The aqueous phase was acidified with concentrated HCl until pH to 1.0–2.0 (some white precipitate formed, which could be removed by filtration); and was extracted with EtOAc five times. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to yield the crude product. The product was purified by flash column chromatography (SiO_2, hexane:EtOAc:formic acid, 25:10:1) to afford 0.95 g (96%) of a pale yellow solid. ^{1}H NMR ($CDCl_3$), δ: 2.86–2.97 (dd, $J=7.0$, 18.7 Hz, 2H), 5.17–5.25 (t, $J=8.4$, 6.1 Hz, 2H), 5.76–5.81 (t, $J=8.4$, 7.3 Hz, 1H), 6.99 (s, 1H), 7.15 (s, 1H), 7.25 (s, 1H); ^{13}C NMR ($CDCl_3$), δ: 45.27, 77.03, 120.60, 124.71, 125.52, 127.20, 131.05, 144.87, 178.33. HRMS: calcd for $C_9H_9O_3S$ (M–1): 197.0273. Found: 197.0275.