

Carbonyl and olefin reactivities for the Baylis–Hillman reaction of fluorocarboxyls

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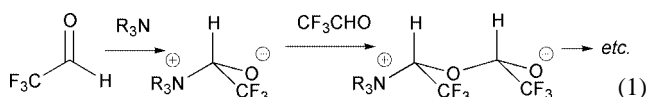
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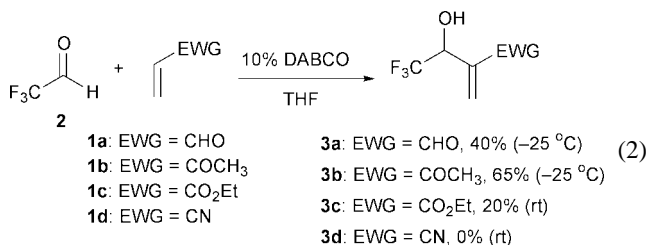
The product formation and yields for the Baylis–Hillman reaction of fluorine-containing carbonyl compounds depend on a balance between the reactivities of the carbonyl and olefin partners.

It is well established that the biological properties of medicinal compounds can often be influenced by fluorine substitution.¹ The physical properties of several electronic and optical devices also depend immensely on the structure of fluoroorganic molecules.² Fluorine substitution provides organic chemists with an opportunity to study an extreme case of electronic effect in reactions.^{1,2} As part of our ongoing projects in fluoroorganic chemistry,³ we examined the Baylis–Hillman (BH) reaction⁴ of activated olefins with fluoro-aldehydes and -ketones in the



presence of 10 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO). Herein we report a fascinating relation between the reactivities of the carbonyl and olefin partners for the BH reaction of fluorocarboxyls; a match providing optimum yields of the products, whereas a mismatch resulting in the decomposition or side reaction of the faster reacting partner.

Acrolein (**1a**), methyl vinyl ketone (**1b**), ethyl acrylate (**1c**) and acrylonitrile (**1d**) were the olefins chosen for the reaction. Initially we studied the reaction of fluoral (**2**) with **1a–d**. Upon mixing **2** with **1a** at rt under neat conditions, in the presence of 10% DABCO, polymerization of both reactants occurred. Both of these are known to polymerize in the presence of amines [eqn. (1)].^{5,6} We then carried out the reaction in THF and obtained a very low yield of the expected product along with the polymerized starting materials. With the hope of arresting the polymerization, we lowered the reaction temperature to $-25\text{ }^{\circ}\text{C}$ and obtained a 40% yield of the product, **3a** [eqn. (2)]. However,



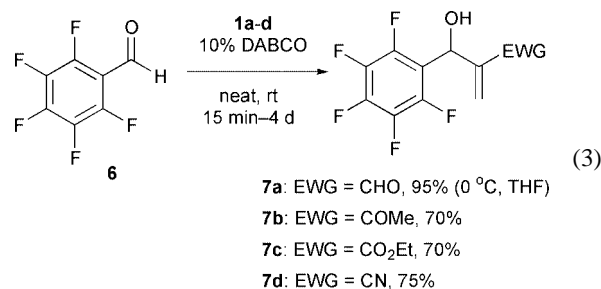
we could not suppress the polymerization completely. Further lowering the temperature had a deleterious effect since polymerization of both reactants was faster than the BH reaction at this temperature.

Reaction of **2** with **1b** provided the product **3b** in 35% yield under neat conditions, at rt, 1 h. Surprisingly, the yield in THF at $-25\text{ }^{\circ}\text{C}$ was 65%! [eqn. (2)]. However, the reaction of **1c** provided only a 20% yield of the product **3c** at rt under neat conditions [eqn. (2)]. Decreasing the reaction temperature suppressed the BH reaction completely and only the polymer of

fluoral was obtained. Olefin **1d** did not yield any BH product **3d** at room or lower temperature.

Reaction of 2,2,3,3,4,4,4-heptafluorobutanal (**4**), the fluorinated homolog of **2**, showed identical reaction patterns with slightly improved yields of the products. Thus, while **1a** and **1b** provided 50 and 70% yield, respectively, of products at $-25\text{ }^{\circ}\text{C}$, **1c** provided 22% yield of the product **5c** and **1d** failed to provide any product at rt.

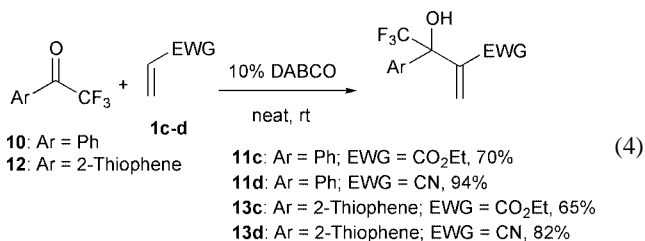
The dissimilarity in product yields from activated olefins of differing reactivity captivated us. We considered a less reactive perfluorinated aldehyde that does not undergo polymerization in the presence of a 3^o-amine and tested pentafluorobenzaldehyde (**6**) with **1a–d**. While the reactions of **1b–d** were complete under neat condition at rt within 2–4 d, **1a** polymerized. However, it reacted in THF at $0\text{ }^{\circ}\text{C}$ within 15 min providing 95% yield of the product [eqn. (3)].



Ordinary ketones undergo Baylis–Hillman reaction occasionally under high pressures⁴ and activated carbonyls, such as α -keto esters and hexafluoroacetone undergo relatively fast reaction.^{7,8} 1,1,1-Trifluoroacetone (**8**) is known to trimerize in the presence of amines.⁹ However, our partial success with **2** persuaded us to carry out its reaction at low temperatures. In fact, we obtained only 10–12% yield of the products **9a** with **1a** in THF at $-25\text{ }^{\circ}\text{C}$, and **9d** with **1d** at rt. Olefins **1b** and **1c** failed to provide any product with **8**. We isolated a polymeric material in both of these cases.

To avoid the polymerization initiated by abstraction of the α -hydrogen atom, we focused our attention on aromatic trifluoromethyl ketones. The treatment of 2,2,2-trifluoroacetophenone (**10**) with two equiv. of **1a**, under neat conditions, at rt did not provide any product. Decreasing the reaction temperature to $-25\text{ }^{\circ}\text{C}$ yielded 15% of acrolein dimer along with its polymer. Olefin **1b** also did not provide any of the expected BH products at rt, although we obtained a 30% yield of the dimer. Lowering the temperature resulted only in the suppression of the dimerization. In contrast, a slow reaction (7 d) between **10** and **1c** resulted in 70% yield of the expected allylic alcohol **11c**. The reaction with **1d** was faster, complete within 24 h, and provided 94% yield of the product **11d** [eqn. (4)].

2-(Trifluoroacetyl)thiophene (**12**) provided similar results. On testing with **1a–d**, it underwent reaction only with **1c** within 7 d providing the product **13c** in 65% yield, and with **1d**, within 24 h, providing the product allylic alcohol **13d** in 82% yield [eqn. (4)].



2,3,4,5,6-Pentafluoroacetophenone (**14**) behaved like an ordinary ketone, failing to react with any of the four activated olefins.

In conclusion, we have studied the effect of fluorine substitution in the Baylis–Hillman reaction. A series of novel functionalized fluorinated allyl alcohols have been synthesized during this study, enriching fluoroorganic chemistry.¹⁰ We have successfully obtained products even from amine-sensitive carbonyls as well as olefins by controlling the reaction conditions. This is the first report of a Baylis–Hillman reaction at such low temperatures (−25 °C).

When the fluorocarbonyls are extremely reactive, capable of reacting with themselves in the presence of an amine (*e.g.* fluoral, heptafluorobutanal), the olefin has to be very reactive as well (*e.g.* acrolein, methyl vinyl ketone) to obtain the products. A mismatch as in the case of relatively less reactive ethyl acrylate and acrylonitrile results in the polymerization of these fluoroaldehydes. The reaction of a less reactive fluorocarbonyl, such as pentafluorobenzaldehyde, is effective with both highly reactive and moderately reactive olefins. Decreasing the reactivity of the fluorocarbonyl further (*e.g.* 2,2,2-trifluoroacetophenone) provides good yield of products only with the less reactive olefins (*e.g.* ethyl acrylate and acrylonitrile). Ring-fluorination of aromatic ketones does not sufficiently activate the carbonyl for the reaction. It appears that a match between the reactivities of the fluorocarbonyl and olefin partners is essential for obtaining reasonable yield of the products in the Baylis–Hillman reaction.¹¹

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Notes and references

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- The reaction of methyl vinyl ketone with fluoral is representative. 2,2,2-Trifluoroacetaldehyde (0.49 g, 5 mmol) was added, at −25 °C, to a stirred solution of methyl vinyl ketone (0.70 g, 10 mmol, 0.83 mL) in THF (5 mL). DABCO (0.056 g, 0.5 mmol) in 0.5 mL THF was added to this and was stirred at this temperature for an additional hour. The solvent was evaporated under vacuum, and the crude reaction mixture was purified by silica gel chromatography (hexanes–ethyl acetate 9:1) to yield 0.55 g (65%) of the pure product.