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# Nickel(0)-catalyzed coupling of vinylzirconiums to α-bromo-α,α-difluoro esters. Convenient generation of a functionalized allyldifluoro moiety

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## Abstract

Vinylzirconium reagents couple with α-bromo-α,α-difluoro esters in the presence of a $Ni(PPh_3)_4$ catalyst to form alkenyl difluoro esters in good yields. This reaction exemplifies a novel mode of reactivity for α-bromo-α,α-difluoro esters wherein the inherent electrophilicity of the carbon–bromine bond is utilized in the course of the reaction rather than being formally reduced in Reformatzsky-type reactions. The choice of ester group in the reactant is critical to the success of this reaction with the isopropyl group, formed via a novel transesterification procedure, giving the best yields. © 2000 Elsevier Science Ltd. All rights reserved.

Fluorinated compounds play an important role in medicinal chemistry and improved methods for their synthesis are in constant demand. As early as 1990, fluorinated derivatives of arachidonic acid were shown to be inhibitors of PGH synthase indicating that alkenyldifluoro groups could have applications in drug-like molecules.[1] However, the existing synthetic methods only allow alkenyldifluoro incorporation into a few, often perfluorinated, molecules. Ethyl bromodifluoroacetate **1** offers a convenient starting material that already contains the desired fluorines and could allow the preparation alkenyldifluoro esters via displacement of the bromine. Additionally, the product of this coupling could be further derivatized via the ester functionality giving a flexible synthesis for a range of products.

α-Bromo-α,α-difluoro esters have been used in organometallic reactions where the bromine is typically converted into a zinc or copper species which can then react with activated electrophiles.[2] In order to incorporate the difluoroalkenyl group into a variety of molecules, we envisioned an alternate approach where a metallated species, derived from readily available acetylenes, would directly couple to the difluoro carbon via a displacement of the bromine.[3] By this means, one could directly synthesize compounds that had an alkenyldifluoro moiety from commercially available materials, with the potential for further elaboration via the remaining ester group (Scheme 1).

We initially examined the use of the bromoester **1** in palladium-catalyzed coupling reactions with vinyl zirconium and vinyl aluminum reagents derived from acetylenes.[4] However, with a host of palladium catalysts, we found no coupling with vinyl alanes, alanates and vinyl zirconiums under any condition.

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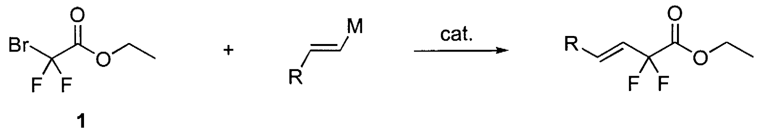
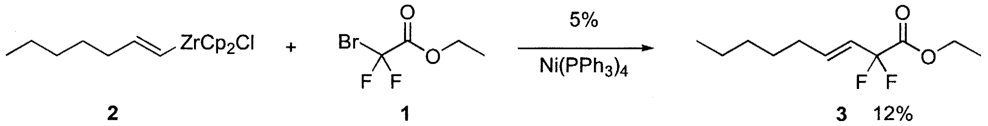


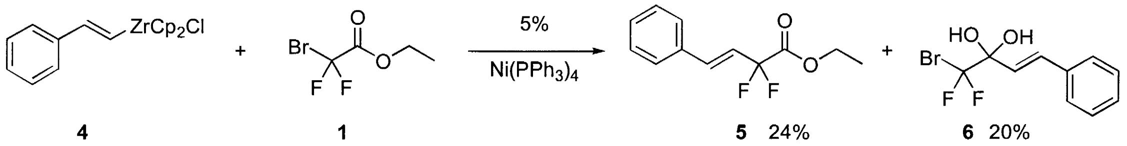
Scheme 1.

It was not until we used ethyl iododifluoroacetate that we were able to observe any product formation, albeit in trace amounts.[5] When we changed the catalyst to $Ni(PPh_3)_4$ we were able to insert into the carbon–bromine bond and catalytically promote the coupling of the vinyl zirconium **2** to form the allylic difluoride **3**, in low yield (Scheme 2).[6] With vinyl alanes and alanates, no coupling was observed.



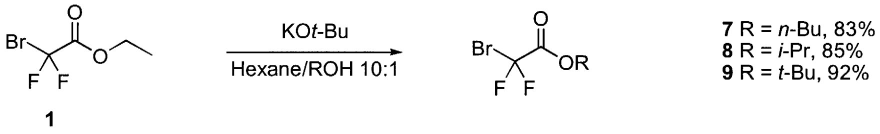
Scheme 2.

We then used the vinyl zirconium reagent derived from phenylacetylene as the substrate to examine the conditions needed to couple to α-bromo-α,α-difluoro esters. Although coupling to form **5** was observed under most conditions with $Ni(PPh_3)_4$, other nickel catalysts such as $Ni(acac)_2$ failed either to promote coupling or resulted in decomposition of the reaction mixture ($Ni(COD)_2$). Product yields still suffered due to addition of the vinyl zirconium to the ester carbonyl to form **6,** identified by its mass spectra (Scheme 3).



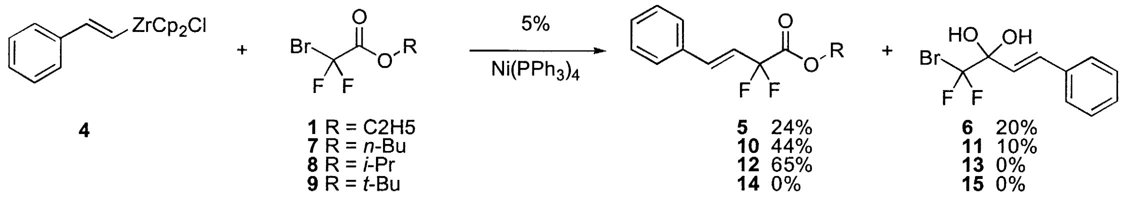
Scheme 3.

To reduce the undesired attack sterically hindered esters were introduced. Unfortunately, several published procedures for the formation of the desired α-bromo-α,α-difluoro esters involve long reaction schemes and toxic reagents.[7] As ethyl bromodifluoroacetate is commercially available we explored a direct transesterification to synthesize these normally difficult to prepare esters. After examining a wide range of conditions, we found that use of a catalytic amount of potassium *tert*-butoxide in a 10:1 mixture of hexane and the alcohol afforded the esters cleanly and in high yield.[8] On a large scale (20 g) the workup was crucial, utilizing concentrated HCl to quench the reaction mixture followed by addition of water and extraction with hexanes. This quickly and cleanly afforded the α-bromo-α,α-difluoro esters **7**–**9** needed to examine the steric influence on the attack on the ester carbonyl (Scheme 4).



Scheme 4.

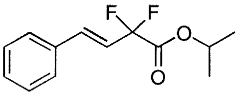
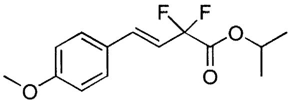
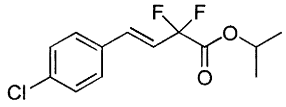
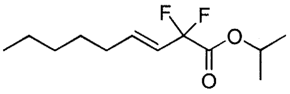
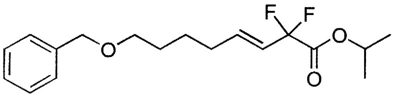
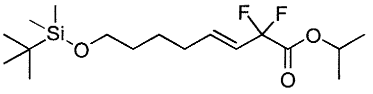
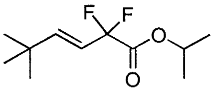
Using the vinyl zirconium reagent **4** derived from phenylacetylene, the coupling reaction was then carried out each with three sterically hindered esters, **7**–**9**. This led to an improvement using the *n*-butyl ester **7** over the ethyl ester, however, the isopropyl ester **8** seemed to eliminate the byproduct **13** completely. Interestingly, no coupling was observed using the *tert*-butyl ester **9** even with aliphatic vinyl zirconium reagents (Scheme 5).



Scheme 5.

With the isopropyl ester, we examined a variety of substrates as coupling partners. The results can be seen in Table 1. While good yields were obtained with aryl vinyl zirconium reagents, aliphatic vinyl zirconium reagents (entries 4–6) gave poorer yields, still suffering from attack on the ester carbonyl carbon. This suggests that the degree of attack on the ester carbonyl carbon is also dependent on the size of the vinyl zirconium reagent. Additionally, slower coupling could presumably result in simple reduction of the α-bromo-α,α-difluoro ester, yielding a volatile component of the reaction mixture.

Table 1

| Entry | Product | Yield | $^{19}$F Shift (ppm)* | $J_{\text{F-Ha}}$ (Hz) |
|---|---|---|---|---|
| 1 |  | 65 | -27.61 | 9.6 |
| 2 |  | 53 | -26.97 | 13.2 |
| 3 |  | 45 | -27.66 | 16.2 |
| 4 |  | 39 | -27.18 | 11.4 |
| 5 |  | 27 | -27.32 | 12.2 |
| 6 |  | 24 | -27.29 | 12.2 |
| 7 |  | 50 | -27.15 | 9.9 |

* Referenced to TFA

In a typical procedure, a 25 mL round-bottomed flask is charged with zirconocene hydrochloride (Schwartz' reagent, 260 mg, 1 mmol) and placed under alternating vacuum/argon 5× and then suspended in 3 mL THF. Phenylacetylene is then added via syringe (110 μL, 1 mmol) and the mixture is stirred in the dark (covered with aluminum foil), under argon for 30 min. In a separate 10 mL flask, dichloro(bistriphenylphosphine)nickel II (33 mg, 0.05 mmol) and triphenylphosphine (26 mg, 0.01

mmol) are thoroughly degassed and then suspended in 1 mL THF under argon. *n*-Butyllithium is then added dropwise (40 μL, [2.5 M in hexanes], 0.01 mmol) and the red mixture is allowed to stir for an additional 5 min. The catalyst is then added via cannula simultaneously with isopropyl bromodifluoroacetate (325 mg, 1.5 mmol) diluted in THF (0.5 mL) to the vinyl zirconium at room temperature. The final mixture is allowed to stir for 1 h at room temperature, then quenched with 1M HCl (5 mL) and extracted with ethyl acetate (3×20 mL). The combined organic extracts are washed with brine (2×10 mL), dried over magnesium sulfate, filtered over a pad of silica gel (10×30 cm) eluting with ethyl acetate and concentrated in vacuo. The resulting clear oil is then purified by column chromatography on silica gel, 2:98 ethyl acetate:hexanes to afford **12** as a clear oil (156 mg, 0.65 mmol, 65%). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.40 (m, 5H), 7.08 (dt, *J*=16.2, 2.7 Hz, 1H), 6.30 (dt, *J*=16.2, 11.4 Hz, 1H), 5.17 (septet, *J*=6.3 Hz, 1H), 1.34 (d, *J*=6.3 Hz, 6H); $^{19}$F NMR ($CDCl_3$, TFA) $\delta$ −27.61 (d, *J*=9.6 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 136.73 (t, *J*=9.2 Hz), 134.20, 129.57, 128.82, 127.41, 71.38, 21.52; GC-MS 240 (15), 153 (100), 133 (65).

Thus, we have demonstrated a novel reactivity pattern for α-bromo-α,α-difluoro esters that does not involve a formal reduction of the carbon–bromine bond. Allowing the α-carbon to react as an electrophile greatly increases the utility of α-bromo-α,α-difluoro esters, promising a wide range of products. Furthermore, we have synthesized a variety of α-bromo-α,α-difluoro esters using a novel transesterification protocol directly from ethyl bromodifluoroacetate in excellent yields.

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8. Experimental Procedure: Ethylbromodifluoroacetate (5.0 g, 24.6 mmol) is added to a mixture of dry isopropanol (35 mL) and hexanes (300 mL) and the resulting mixture is chilled to 0°C. Potassium *tert*-butoxide (394 mg, 3.5 mmol) is then added in two equal portions 5 min apart (the potassium *tert*-butoxide must be very dry otherwise the reaction stops) and the mixture is allowed to stir for 1 h. The reaction is then quenched with conc. HCl (30 mL), then washed with water (2×50 mL) and brine (1×50 mL), then dried with $MgSO_4$ and filtered over a pad of silica gel (7×5 cm), eluting with 10% $Et_2O$/hexanes. The solvent is carefully removed in vacuo at 0°C yielding the isopropyl ester as a clear oil (4.52g, 85%). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.20 (septet, *J*=6.6 Hz, 1H), 1.38 (d, *J*=6.6 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 159.53 (t, *J*=31 Hz), 109.01 (t, *J*=313 Hz), 71.47, 21.22; GC-MS 217 (5), 203 (25), 131 (100), 109 (35).