ORGANIC
LETTERS

2006
Vol. 8, No. 6
1109−1111

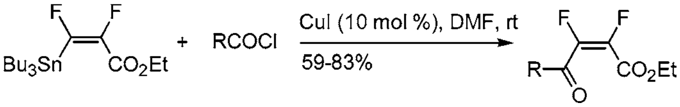
# Copper(I)-Only Catalyzed Reactions of (*E*)-2,3-Difluoro-3-stannylacrylic Ester with Acid Chlorides and Mechanistic Studies of the “Copper Effect” in Stille Coupling Reactions

**Yi Wang and Donald J. Burton***

*Department of Chemistry, University of Iowa, Iowa City, Iowa 52242*
*donald-burton@uiowa.edu*

**Received December 13, 2005**

## ABSTRACT



**The reactions of (*E*)-2,3-difluoro-3-stannylacrylic ester with acid chlorides under catalysis of CuI stereospecifically afforded ethyl (2*Z*)-2,3-difluoro-4-oxo-substituted 2-butenoates in good yields. Moreover, direct spectroscopic observation of the corresponding organocopper reagent was observed for the first time in Stille coupling reactions of organostannanes.**

The Stille cross-coupling reaction of organostannanes and organic electrophiles is a powerful carbon−carbon bond formation reaction in synthetic organic chemistry.[1] The use of cocatalytic copper(I) in Stille coupling reactions is well documented.[2−6] Nevertheless, the role of copper(I) has not been unequivocally determined. The beneficial use of copper(I) as a scavenger for free phosphine ligands was suggested by Farina and Liebeskind.[3,4] However, in highly polar solvents, the rate-accelerating effect of copper(I) has been attributed to a preliminary transmetalation of the organostannane to generate a more reactive organocopper intermediate.[3−5,7] Recently, Baldwin and co-workers utilized this concept and demonstrated that the combination of a copper(I) salt and cesium fluoride can significantly enhance Stille coupling reactions.[8] However, the formation of the presumed organocopper species has never been directly observed in these reactions. As part of our ongoing investigation for the introduction of *cis*-difluoroethenyl units into organic molecules,[9] we wish to report the Cu(I)-mediated coupling reactions of (*E*)-2,3-difluoro-3-stannylacrylate **1**[9d] with acid chlorides as the first synthetic route to *cis*-difluoro-substituted analogues of 4-oxo-2-butenoates, which have been widely used as intermediates in organic synthesis[10] and pharmaceutical agents[11] and, more importantly, to the best of our knowledge, the first direct spectroscopic observation of the organocopper intermediate in Stille coupling reactions.

Although Stille reported that $Pd(PPh_3)_4$ alone catalyzed the coupling reaction of vinylstannanes and acid chlorides,

---

[1] For reviews, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771−1780. (c) Mitchell, T. N. *Synthesis* **1992**, 803−815.

[2] Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364.

[3] Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911.

[4] Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305−1309.

[5] Han, X.; Stolz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.

[6] Lu, L.; Burton, D. J. *Tetrahedron Lett.* **1997**, *38*, 7673−7676.

[7] Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78.

[8] Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132−1136.

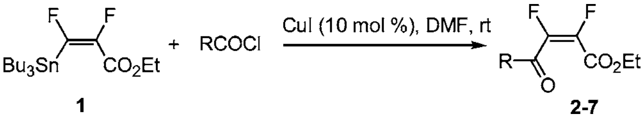
[9] (a) Spawn, T.; Heinze, P.; Bailey, A.; Shin-Ya, S.; Burton, D. J. *J. Fluorine Chem.* **1988**, *38*, 131−134. (b) Davis, C. R.; Burton, D. J. *J. Org. Chem.* **1997**, *62*, 9217−9222. (c) Fontana, S. A.; Davis, C. R.; He, Y.; Burton, D. J. *Tetrahedron* **1996**, *52*, 37−44. (d) Wang, Y.; Lu, L.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 10743−10746.

[10] (a) Lopez-Pedrosa, J.; Pitts, M. R.; Roberts, S. M.; Saminathan, S.; Whittall, J. *Tetrahedron Lett.* **2004**, *45*, 5073−5075. (b) Alibes, R.; Busque, F.; De March, P.; Figueredo, M.; Font, J.; Parella, T. *Tetrahedron* **1998**, *54*, 10857−10878. (c) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339−4341. (d) Russell, G. A.; Kim, B. H. *Synlett* **1990**, 87−88. (e) Stetter, H.; Jonas, F. *Chem. Ber.* **1981**, *114*, 564−580.

10.1021/ol053023x CCC: $33.50

no coupling reaction between **1** and benzoyl chloride was observed when $Pd(PPh_3)_4$ was used alone (rt/overnight). Under Liebeskind conditions[3,6] [5 mol % of $Pd(PPh_3)_4$ and 10 mol % of CuI], the desired product was formed in moderate yield (∼40%), which could not be separated pure from byproducts by column chromatography. Surprisingly, in the absence of the palladium catalyst, a very clean reaction was observed, based on $^{19}F$ NMR analysis of the reaction mixture, and the pure desired product was readily obtained in 75% yield.[12] A variety of acid chlorides were studied, and all gave satisfactory results. These results are summarized in Table 1.

**Table 1.** Reactions of **1** with Acid Chlorides



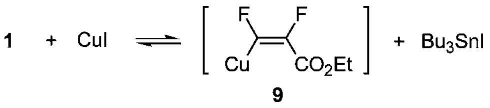
| entry | RCOCl | product | yield[a] (%) |
|---|---|---|---|
| 1 | $C_6H_5COCl$ | ($Z$)-$C_6H_5COCF{=}CFCO_2Et$ (**2**) | 75 |
| 2 | $p$-$O_2NC_6H_4COCl$ | ($Z$)-$p$-$O_2NC_6H_4COCF{=}CFCO_2Et$ (**3**) | 70 |
| 3 | $n$-$C_9H_{19}COCl$ | ($Z$)-$n$-$C_9H_{19}COCF{=}CFCO_2Et$ (**4**) | 83 |
| 4 | $p$-$MeOC_6H_4COCl$ | ($Z$)-$p$-$MeOC_6H_4COCF{=}CFCO_2Et$ (**5**) | 67 |
| 5 | $Me_3CCOCl$ | ($Z$)-$Me_3CCOCF{=}CFCO_2Et$ (**6**) | 59 |
| 6 | $p$-$IC_6H_4COCl$ | ($Z$)-$p$-$IC_6H_4COCF{=}CFCO_2Et$ (**7**) | 60 |

[a] Isolated yield based on **1**.

Both aromatic and aliphatic acid chlorides worked well. The coupling reactions were not affected by the presence of either electron-withdrawing or electron-donating groups on the aromatic ring. When a sterically hindered aliphatic acid chloride such as pivaloyl chloride was employed as substrate, the reaction occurred smoothly to give the product in good yield. Thus, this method offered a facile synthetic route to ethyl (2$Z$)-2,3-difluoro-4-oxo-substituted 2-butenoates.

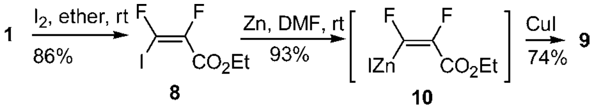
After the successful coupling reaction of **1** with acid chlorides with copper(I) catalysis, we turned our focus to the role of copper(I) in the reactions summarized in Table 1. An initial experiment indicated that copper(I) is crucial in these reactions. In the absence of copper(I), no coupling product was formed from the mixture of **1** and benzoyl chloride in DMF, and only slow reduction of **1** was observed (i.e., 29% of (2$Z$)-$CHF{=}CFCO_2Et$ was formed after 6 h at rt). Moreover, $^{19}F$ NMR analysis of the reaction mixture after 3 h at rt showed that treatment of **1** with a stoichiometric amount of copper(I) iodide gave an apparent equilibrium mixture consisting of **1** and the presumed organocopper species **9**[13] in a ratio of 1.3:1, along with 1% of the homocoupled product of **1** and 3% of the reduction product of **1** (normalized $^{19}F$ NMR yield), and after another 33 h at rt, the ratio of **1** and **9** changed to 1:1.1. The proposed equilibrium[14] is illustrated in Scheme 1.

### Scheme 1



The presumed presence of the organocopper species was confirmed by comparison with an independent preparation of the copper reagent from the corresponding zinc reagent,[16] as illustrated in Scheme 2.

### Scheme 2



Treatment of **1** with $I_2$ afforded ethyl (2$E$)-2,3-difluoro-3-iodoacrylate **8**, which when treated with zinc dust gave the corresponding zinc reagent **10** in 93% $^{19}F$ NMR yield with an 86:14 ratio of the mono- and bis-fluoroalkenylzinc reagents[17] (by $^{19}F$ NMR analysis of the reaction mixture, vs $PhCF_3$ as internal standard). Subsequently, treatment of **10** with stoichiometric CuI afforded **9** in 74% $^{19}F$ NMR yield, whose chemical shifts matched exactly with the presumed organocopper species in the equilibrium mixture of **1** and CuI. The resultant copper reagent **9** reacted with benzoyl chloride to give the coupling product in ∼30% $^{19}F$ NMR yield.

On the basis of transmetalation from the organotin compound to the organocopper intermediate and a proposed

---

[11] (a) Miles, H.; Yurjevich, S. S.; Petrovna, K. O.; Valentinovna, P. E.; Goun, E. A. U.S. Patent 6602907, 2003. (b) Koz'minykh, V. O.; Milyutin, A. V.; Makhmudov, R. R.; Belyaev, A. O.; Koz'minykh, E. N. *Pharm. Chem. J.* **2004**, *38*, 665−669. (c) Shikawa, K.; Nagase, T.; Ihara, M.; Nishikibe, M. PCT Int. Appl. WO 9623773, 1996. (d) Bianchi, M.; Barzaghi, F. *Ger. Offen.* DE 3239209, 1983.

[12] **Procedure for the Preparation of Ethyl (2$Z$)-2,3-Difluoro-4-oxo-4-phenylbut-2-enoate (2).** To a mixture of CuI (0.01 g, 0.05 mmol) and benzoyl chloride (0.06 mL, 0.52 mmol) in 3 mL of dry DMF was added **1** (0.21 g, 0.50 mmol) under $N_2$. The mixture was stirred at room temperature for 6 h. $^{19}F$ NMR analysis of the reaction mixture showed that the reaction was complete. The mixture was purified by column chromatography (hexane/ethyl acetate = 5:1), and 0.09 g of yellow oil was obtained: $^{19}F$ NMR ($CDCl_3$) $\delta$ −121.5 (d, $J = 3.9$ Hz, 1 F), −146.8 (d, $J = 3.9$ Hz, 1 F); $^{1}H$ NMR ($CDCl_3$) $\delta$ 7.98 (dm, $J = 8.4$ Hz, 2 H), 7.70−7.65 (tt, $J = 7.5$, 1.3 Hz, 1 H), 7.56−7.51 (tm, $J = 7.6$ Hz, 2 H), 4.13 (q, $J = 7.1$ Hz, 2 H), 1.05 (t, $J = 7.2$ Hz, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 184.2 (d, $J = 21.8$ Hz), 159.2 (dd, $J = 29.2$, 7.5 Hz), 149.1 (dd, $J = 281.6$, 11.5 Hz), 139.1 (dd, $J = 266.5$, 15.3 Hz), 135.0, 134.4 (d, $J = 2.3$ Hz), 129.4 (d, $J = 0.5$ Hz), 129.1, 62.6, 13.5; HRMS calcd 240.0598 for $C_{12}H_{10}F_2O_3$, found 240.0598.

[13] Chemicals shifts of **9** are located at −100 and −146 ppm, whereas the chemical shifts of **1** are located at −116 and −138 ppm, respectively.

[14] Previous work in our laboratory had shown that fluorinated vinylcopper reagents reacted with chlorotrialkylstannanes to produce fluorinated vinylstannanes.[15,16b] The work reported in ref 16b also suggested an equilibrium process.

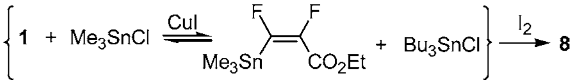
[15] Blumenthal, E. J. Ph.D. Thesis, University of Iowa, Iowa City, IA, 2000, p 104.

[16] (a) Burton, D. J.; Hansen, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 4229−4230. (b) Burton, D. J.; Jairaj, V. *J. Fluorine Chem.* **2004**, *125*, 673−680. For reviews of fluorinated alkenylzinc and alkenylcopper reagents, see: (c) Burton, D. J.; Yang, Z.; Morken, P. A. *Tetrahedron* **1994**, *50*, 2993−3063. (d) Burton, D. J.; Lu, L. In *Topics in Current Chemistry*; Chambers, R. D., Ed.; Springer: Berlin, 1997; Vol. 193, pp 45−89.

[17] Chemical shifts of **10** are located at −114 and −145 ppm for the bis and −116 and −144 ppm for the mono reagent, respectively.

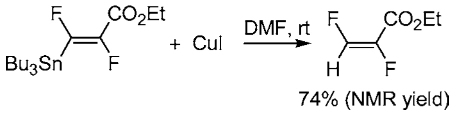
equilibrium between them, addition of another tin chloride would generate another tin ester. In the absence of CuI, no reaction was observed between **1** and $Me_3SnCl$ in DMF. However, a mixture of **1**, CuI (10 mol %), and $Me_3SnCl$ in DMF gave a mixture of the trimethyltin ester and **1** with a ratio of 1:10 after 2 h at rt.[18] The presence of two tin esters was further confirmed by formation of the iodoester **8** via treatment of the mixture with iodine (Scheme 3).

**Scheme 3**



However, when the corresponding (*Z*)-2,3-difluoro-3-stannylacrylate was treated with benzoyl chloride under similar reaction conditions, no coupling product was observed. The *trans* tin ester was consumed completely, and the reduction product (*trans*-$CHF{=}CFCO_2Et$) was formed in 74% $^{19}F$ NMR yield (Scheme 4). Our attempt to independently prepare the *trans* analogue of copper reagent was not successful. Loss of fluorine signal was observed when the *trans* analogue of the zinc reagent was treated with stoichiometric CuI. Apparently, the *trans* analogue of copper reagent is not stable in our case. The stability of *cis* copper reagent is presumably attributed to the coordination[19] between copper and oxygen of ester group in **9**.

**Scheme 4**



In summary, ethyl (2*Z*)-2,3-difluoro-4-oxo-substituted 2-butenoates were prepared stereospecifically for the first time in good yields via the reaction of **1** with acid chlorides with CuI catalysis. In addition, via $^{19}F$ NMR spectroscopy, we were able to directly observe the presence of the organocopper intermediate for the first time in Stille coupling reactions. The formation of the organocopper species directly from the organostannane, at least in our case, opens up new possibilities in organotin chemistry, e.g., the cross-coupling reaction of organostannanes promoted by copper(I) salts only. Other publications have also suggested that Cu(I)-mediated coupling reactions from organostannanes may become synthetically important.[20−23]

**Acknowledgment.** We acknowledge the National Science Foundation for their financial support of this work.

**Supporting Information Available:** Experimental procedure for the synthesis of **3**−**8** and their characterization by $^1H$, $^{19}F$, and $^{13}C$ NMR and HRMS; copies of $^1H$, $^{19}F$, and $^{13}C$ NMR of compounds **2**−**8**; copy of the $^{19}F$ NMR of the reaction mixture of **1** with CuI; copies of the $^{19}F$ NMR of **9**, **10**, and mixture of the two tin esters. This material is available free of charge via the Internet at http://pubs.acs.org.

OL053023X

---

(18) Chemical shifts of the trimethyltin ester are located at −118 and −139 ppm. Our attempt to synthesize the pure compound was not successful due to decomposition of the trimethyltin analogue on silica gel.

(19) (a) Shen, Y.; Ruffer, T.; Schulz, S. E.; Gessner, T.; Wittenbecher, L.; Sterzel, H.; Lang, H. *J. Organomet. Chem.* **2005**, *690*, 3878−3885. (b) Pampaloni, G.; Peloso, R.; Graiff, C.; Tiripicchio, A. *Organometallics* **2005**, *24*, 4475−4482.

(20) Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609−3610.

(21) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973−5982.

(22) Kang, S.; Kim, J.; Choi, S. *J. Org. Chem.* **1997**, *62*, 4208−4209.

(23) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.