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Wittig reaction of formyl-substituted organotrifluoroborates and stabilized phosphonium ylides in an aqueous medium

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Abstract

The synthesis of unsaturated organotrifluoroborates using the Wittig alkenation is described. These transformations to disubstituted alkenes were achieved by using formyl-substituted organotrifluoroborates and stabilized ylides using water as a solvent. The products were isolated in moderate to excellent yields and the reaction gave preferentially the *E*-isomer.

Green technology is a topic that is receiving significant attention because of environmental issues.[1] The development of methods focusing on environmentally benign reaction media has been particularly prominent.[2] Thus, advances in the development of aqueous biphase catalysis[3] and the use of supercritical fluids,[4] ionic liquids,[5] and fluorous media[6] continue to be important areas of investigation.

Wittig[7] and Horner–Wadsworth–Emmons[7a,8] (HWE) reactions have been widely used in synthesis as a means of elaborating the carbon skeleton and introducing further functional groups into organic substrates. The generality and high stereoselectivity of these reactions constitute two desirable features offered by these protocols. Additionally, the double bond geometry can generally be predicted and controlled by choosing the appropriate reagents and reaction conditions. Many novel and useful adaptations of the Wittig reaction have been described in the literature, including those employing microwaves,[9] sonication,[10] light irradiation,[11] ionic liquids,[12] silica,[13] lithium salts,[14] benzoic acid,[15] surfactants,[16] phase transfer catalysts,[17] cyclodextrins,[18] and high temperatures[19] or pressures,[20] as well as those employing solvent free conditions.[21]

The use of water as a solvent for Wittig reactions has also been reported in the reaction between aldehydes and stabilized or semistabilized phosphorus ylides.[22] In addition to their environmental benefits, these protocols sometimes provide higher yields and similar diastereoselectivities[22d] when compared to reactions performed in organic solvents.

Organotrifluoroborates have proven to be robust surrogates for boronic acids and boronate esters in Suzuki coupling reactions, providing many advantages over the latter reagents.[23] One of the major benefits is the ability to elaborate upon the structure of a simple, functionalized organotrifluoroborate, increasing its molecular complexity while maintaining the valuable carbon–boron bond for subsequent transformation. Recently, our group described the synthesis of unsaturated potassium organotrifluoroborates via the Wittig and Horner–Wadsworth–Emmons reaction of the corresponding trifluoroborato-substituted benzaldehydes.[24] The complementary process, that is, generation and reaction of potassium [(trifluoroboratophenyl) methyl]triphenylphosphonium ylides with aldehydes, was also described as a novel synthetic method for creating functionalized alkenes.[25]

Herein, we report the Wittig reaction of formyl-substituted organotrifluoroborates with commercially available, carbonyl-stabilized ylide reagents in an aqueous medium.[26] In addition to being more environmentally sound, the use of

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preformed stabilized ylides avoids the removal of inorganic or organic salts during the reaction work-up, facilitating the isolation of the potassium organotrifluoroborate products.

The trifluoroborato-substituted aldehydes were prepared from the corresponding boronic acids following a literature procedure.[27] In initial efforts to evaluate different stabilized ylides we used potassium 2-formylphenyltrifluoroborate as a model substrate. The reaction was studied using standard conditions: 2-formylphenyltrifluoroborate (1.0 mmol) in conjunction with diverse ylides (1.5 mmol) in water (2 mL). In all the cases, the desired alkene was isolated in low yield in incomplete reactions when the reaction was conducted at room temperature, owing to the poor solubility of the reagents. Complete consumption of the starting material was critical not only for the overall efficiency of the method, but also because separation of the product from the organotrifluoroborate starting material is quite difficult. When the reactions were heated to 90 °C, ^{1}H and ^{13}C NMR analysis of the reactions revealed that the reaction was complete after 12 h. To isolate the products, the water was removed under vacuum and the triphenylphosphine oxide and excess ylide were removed by trituration with dichloromethane followed by washing the mixture with acetone. In this manner, the remaining alkene-functionalized organotrifluoroborates **3** were all obtained in moderate to good yields as stable white solids (Table 1).[28]

With the optimized conditions for the formation of the alkenes in hand, we examined the scope of the aqueous Wittig reaction for the synthesis of alkene-functionalized organotrifluoroborates using methyl (triphenylphosphoranylidene)acetate **2a** and various formyl-substituted organotrifluoroborates **1b–g**. The results are depicted in Table 2.

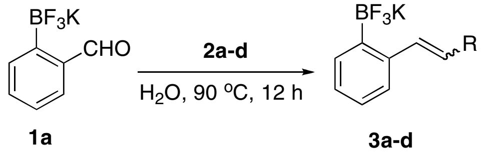
The desired products were obtained in moderate to good yields for a variety of functionalized substrates and substitution patterns, including a heterocyclic aldehyde. Although the degree of diastereoselection proved to be highly variable and substrate-dependent, in all the cases the *E*-isomer was predominant. The lack of high diastereoselectivity is not uncommon in similar Wittig-type reactions performed in aqueous media.[2a–c]

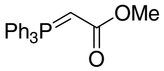
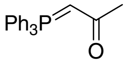
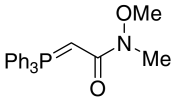
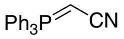
For the most part these trends in diastereoselection translated when the conditions were applied to 1-(triphenylphosphoranylidene)acetone **2b**, although somewhat lower yields and selectivities were observed (Table 3). This might be attributed to the lower reactivity of the ylide that results from greater stabilization of the nucleophile.[7,26] Curiously, aldehyde **1f**, which gave essentially a single diastereomeric enoate on reaction with the corresponding ylide (Table 2, entry 5), gave a nearly 1:1 mixture of *E* and *Z* enone products (Table 3, entry 5).

In summary, we have demonstrated the use of formyl-substituted organotrifluoroborates with carbonyl-stabilized

Table 1

Reaction of 2-formylphenyltrifluoroborate **1a** with different stabilized ylides **2a**–**d** in water at 90 °C



Entry	Ylide		*E*:*Z*[b]	Yield[a] (%)
1		**2a**	80:20	85
2		**2b**	85:15	90
3		**2c**	75:25	65
4		**2d**	60:40	61[c]

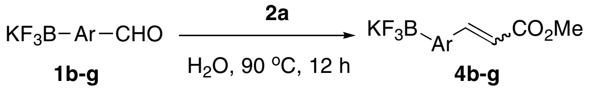
[a] Yield is given for the isolated product, >95% purity unless indicated.

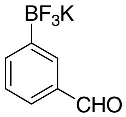
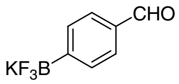
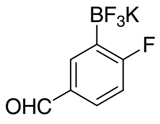
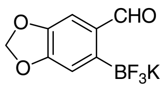
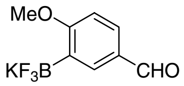
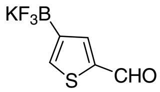
[b] *E*/*Z* ratios were determined by ^{1}H NMR.

[c] 92% pure by NMR.

Table 2

Reaction of formyl-substituted organotrifluoroborates **1b**–**g** with methyl (triphenylphosphoranylidene)acetate **2a** in water at 90 °C

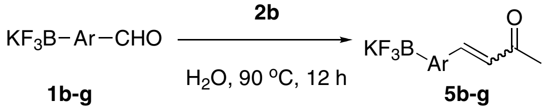


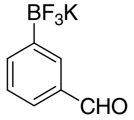
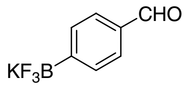
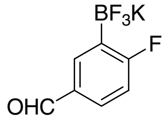
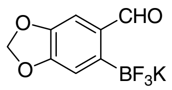
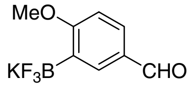
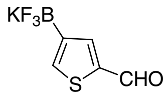
Entry	KF$_3$B-Ar-CHO		*E*:*Z*[b]	Yield[a] (%)
1		**1b**	Only E	82
2		**1c**	70:30	80
3		**1d**	65:35	67
4		**1e**	67:33	65
5		**1f**	Only E	86
6		**1g**	65:35	70

[a] Yield is given for the isolated product, >95% pure by NMR.

[b] *E*/*Z* ratios were determined by ^{1}H NMR.

Table 3
Reaction of formyl-substituted organotrifluoroborates **1b–g** with 1-(triphenylphosphoranylidene)acetone **2b** in water at 90 °C



Entry	KF_3B–Ar-CHO		E:Z[b]	Yield[a] (%)
1		**1b**	Only E	70
2		**1c**	60:40	85
3		**1d**	51:49	60
4		**1e**	52:48	62
5		**1f**	56:44	81
6		**1g**	62:38	69

[a] Yield is given for the isolated product, >95% pure by NMR.
[b] E/Z ratios were determined by ^{1}H NMR.

ylide reagents as a valuable synthetic tool to access E-olefins in moderate to good yields using water as the solvent.

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References and notes

1. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: USA, 2000.
2. (a) Horvath, I. T.; Anastas, P. T. *Chem. Rev.* **2007**, *107*, 2169–2173; (b) Hutchings, G. J. *Catal. Today* **2007**, *122*, 196–200; (c) Kidwai, M. *Pure Appl. Chem.* **2006**, *78*, 1983–1992.
3. (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (b) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3165; (c) Pringle, P. G.; Brewin, D.; Smith, M. B.; Worboys, K. In *Aqueous Organometallic Chemistry and Catalysis*; Horvath, I. T., Joo, F., Eds.; Kluwer Academic: Dordrecht, 1995.
4. Jessop, P. G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: Weinheim, 1999.
5. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (b) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391–1398.
6. *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004.
7. Reviews: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927; (b) Vedejs, E.; Peterson, M. J.. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: New York, 1996; Vol. 2, pp 1–86; (c) Edmonds, M.; Abell, A. In *Modern Carbonyl Olefination Methods and Applications*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 1–17.
8. Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: London, UK, 1980; pp 155–205.
9. (a) Xu, C.; Chen, G.; Fu, C.; Huang, X. *Synth. Commun.* **1995**, *25*, 2229–2233; (b) Spinella, A.; Fortunati, T.; Soriente, A. *Synlett* **1997**, 93–94; (c) Frattini, S.; Quai, M.; Cereda, E. *Tetrahedron Lett.* **2001**, *42*, 6827–6829; (d) Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. *Tetrahedron Lett.* **2004**, *45*, 4401–4404.
10. Silveira, C. C.; Perin, G.; Braga, A. L. *J. Chem. Res., Synop.* **1994**, 492–493.
11. Matikainen, J. K.; Kaltia, S.; Hase, T. *Synlett* **1994**, 817–818.
12. Le Boulaire, V.; Gree, R. *Chem. Commun.* **2000**, 2195–2196.
13. Patil, V. J.; Mavers, U. *Tetrahedron Lett.* **1996**, *37*, 1281–1284.
14. (a) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327–3333; (b) Hooper, D. L.; Garagan, S.; Kayser, M. M. *J. Org. Chem.* **1994**, *59*, 1126–1128.
15. (a) Fliszar, S.; Hudson, R. F.; Salvadori, G. *Helv. Chim. Acta* **1964**, *47*, 159–162; (b) Ruchardt, C.; Panse, P.; Eichler, S. *Chem. Ber.* **1967**, *100*, 1144–1164; (c) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarstrom, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436–1439; (d) Marriott, D. P.; Bantick, J. R. *Tetrahedron Lett.* **1981**, *22*, 3657–3658; (e) Thiemann, T.; Thiemann, C.; Sasaki, S.; Vill, V.; Mataka, S.; Tashiro, M. *J. Chem. Res. Synop.* **1997**, 248–249.
16. Orsini, F.; Sello, G.; Fumagalli, T. *Synlett* **2006**, 1717–1718.
17. Stafford, J. A.; McMurry, J. E. *Tetrahedron Lett.* **1988**, *29*, 2531–2534.
18. Westman, G.; Wennerstrom, O.; Raston, I. *Tetrahedron* **1993**, *49*, 483–488.
19. Fodor, G.; Tomoskozi, I. *Tetrahedron Lett.* **1961**, *2*, 579–582.
20. (a) Nonnenmacher, A.; Mayer, R.; Plieninger, H. *Liebigs Ann. Chem.* **1983**, 2135–2140; (b) Isaacs, N. S.; El-Din, G. N. *Tetrahedron Lett.* **1987**, *28*, 2191–2192.
21. Thiemann, T.; Watanabe, M.; Tanaka, Y.; Mataka, S. *New J. Chem.* **2004**, *28*, 578–584.
22. (a) Wu, J.; Yue, C. *Synth. Commun.* **2006**, *36*, 2939–2947; (b) Wu, J.; Li, D.; Zhang, D. *Synth. Commun.* **2005**, *35*, 2543–2551; (c) Wu, J.; Zhang, D.; Wei, S. *Synth. Commun.* **2005**, *35*, 1213–1222; (d) Dambacher, J.; Zhao, W.; El-Batta, A.; Annes, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett.* **2005**, *46*, 4473–4477.
23. (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286; (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658; (c) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49–56.
24. Molander, G. A.; Figueroa, R. *J. Org. Chem.* **2006**, *71*, 6135–6140.
25. Molander, G. A.; Ham, J.; Canturk, B. *Org. Lett.* **2007**, *9*, 821–824.
26. Vedejs, E.; Peterson, M. J. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1994; Vol. 21.
27. (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027; (b) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460–2470.
28. *Typical procedure*: A mixture of formyl-substituted organotrifluoroborates **1a–e** (1.0 mmol) and the appropriate carbonyl-stabilized ylide **2a–d** (1.5 mmol) was added to a flask followed by the addition of water (2.0 mL). The mixture was heated to 90 °C for 12 h. After this period, the water was removed in vacuo and the residue was washed with dichloromethane (3 × 5.0 mL) and acetone (2 × 5 mL). The products were obtained as white solids after drying under high vacuum.