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Use of Lithium Hexafluoroisopropoxide as a Mild Base for Horner–Wadsworth–Emmons Olefination of Epimerizable Aldehydes

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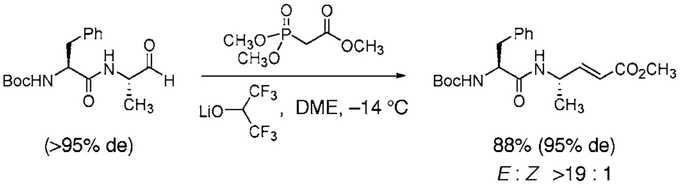
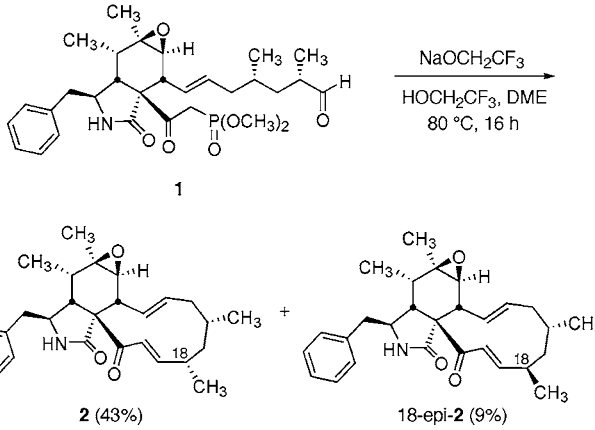
ABSTRACT



The weak base lithium 1,1,1,3,3,3-hexafluoroisopropoxide (LiHFI) is shown to be highly effective as a reagent for intermolecular Horner–Wadsworth–Emmons (HWE) olefination of epimerizable aldehydes with trimethyl phosphonoacetate, affording products with little or no epimerization and notably high *E*-selectivity.

The Horner−Wadsworth−Emmons (HWE) olefination of aldehydes is one of the more reliable carbon−carbon (double) bond-forming reactions in synthesis.[1] Its utility has been extended for applications involving base-sensitive substrates by the introduction of modified protocols.[2] Recently, during the development of a synthetic route to natural products of the cytochalasin family, the intramolecular HWE reaction depicted in Scheme 1 provided a challenging problem whose solution required the development of novel conditions to minimize epimerization of the stereocenter adjacent to the aldehyde group of substrate **1**.[3] As shown in Scheme 1, use of the unusual base sodium trifluoroethoxide (slightly less than 1 equiv) in the presence of trifluoroethanol (TFE, 100 equiv) in 1,2-dimethoxyethane (DME) at 80 °C (16 h) proved optimal in that case to maximize the yield of the cyclized product while minimizing epimerization.[3] This finding prompted us to explore the potential broader utility of fluorinated alkoxides as bases for *inter*molecular HWE

Scheme 1. Optimal Conditions for Intramolecular HWE Cyclization of Cytochalasin Precursor 1.[3]



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[1] (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499. (b) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (c) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (d) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

[2] (a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183. (b) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624. (c) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

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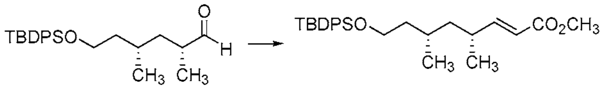
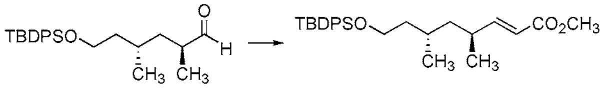
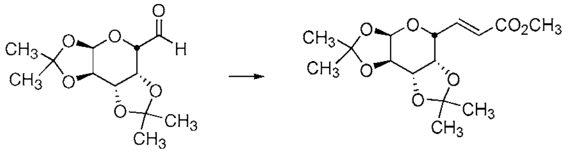
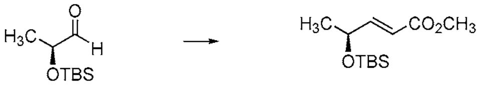
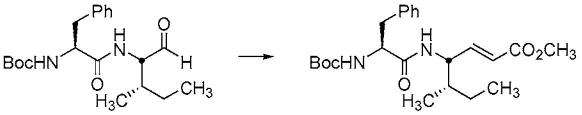
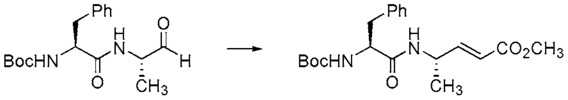
reactions of base-sensitive substrates, leading to the discovery that lithium 1,1,1,3,3,3-hexafluoroisopropoxide (LiHFI) is a nearly ideal reagent in such contexts,[4] as detailed herein.

We first conducted a screen to determine the most effective fluorinated alkoxide for optimal efficiency and *E*-selectivity in the intermolecular HWE reaction of cyclohexanecarboxaldehyde (1 equiv) with trimethyl phosphonoacetate (1.2 equiv). Lithium, sodium, potassium, and cesium salts of the alcohols TFE (pK_a 12.4 in water[4]) and HFI (pK_a 9.3 in water,[4] 1.1 equiv in each case) were investigated as bases, initially using acetonitrile as solvent. LiHFI emerged as the superior reagent, leading to complete conversion of the aldehyde substrate and a high yield of product, with nearly perfect *E*-selectivity. Counterions other than lithium gave reduced *E*-selectivity, and reactions employing 3,3,3-trifluoroethoxide led to partial transesterification of the product with the base. Although LiHFI could be prepared and used as a discrete reagent (a hygroscopic, white solid), invariably we opted for a more convenient procedure involving generation of the base in situ using solutions of *n*-butyllithium and HFI.[5] In addition to acetonitrile, tetrahydrofuran (THF) and DME were also found to be effective solvents. Because DME proved to be slightly advantageous in minimizing epimerization among the most base-sensitive substrates and because it afforded highly reproducible results, we adopted this solvent for routine use. Compiled in Table 1 are our optimized results from a series of experiments using LiHFI as a base for the HWE reaction of trimethyl phosphonoacetate with aldehydes containing an epimerizable α-stereocenter. Also provided for comparison are results with the same substrates using other methods developed for HWE olefination of base-sensitive aldehydes: the Masamune–Roush protocol (LiCl, DBU)[2a] and, in the case of the substrates of the first and final entries, the method of Paterson and co-workers (employing barium hydroxide as base).[2c]

The results of Table 1 show that HWE olefination of a number of epimerizable aldehydes with trimethyl phosphonoacetate (1.2 equiv) using LiHFI (1.18 equiv) as base and DME as solvent is highly efficient and provides products with high *E*-selectivity and little or no epimerization. Of the substrates we investigated, the peptidyl aldehyde of the final entry proved to be the most susceptible to epimerization and provided the greatest distinction among the three protocols examined. With other substrates, existing protocols were quite effective,[2,6] but generally afforded products with somewhat diminished *E*-selectivities. The superior *E*-selectivity of the new protocol for HWE olefination, though not anticipated, proved to be one of its primary advantages. This, plus the extraordinary mildness of the conditions may recommend the new method for use even in cases where epimerization is not an issue.

Table 1. Comparison of Results of HWE Olefination of Epimerizable Aldehydes

substrate de (ee)	reagents[a]	time (h)	product de (ee)	*E*:*Z*[b]	yield[c]
					
98	$LiOCH(CF_3)_2$	19	97	48:1	95
98	LiCl, DBU	72	96	31:1	92[d]
98	$Ba(OH)_2$	52	98	21:1	81[d]
					
96	$LiOCH(CF_3)_2$	15	95	>19:1	94
96	LiCl, DBU	48	89	24:1	91[d]
					
>95	$LiOCH(CF_3)_2$	0.5	>95	>19:1	89
>95	LiCl, DBU	0.2	>95	9:1	80
					
(>95)	$LiOCH(CF_3)_2$	0.7	(>95)	>19:1	77
(>95)	LiCl, DBU	2	(>95)	15:1	74
					
>95	$LiOCH(CF_3)_2$	18	>95	>26:1	94[e]
>95	LiCl, DBU	18	>95	12:1	92[e]
					
>95	$LiOCH(CF_3)_2$	0.8	95	>19:1	88[e]
>95	LiCl, DBU	18	80	7:1	84[e]
94	$Ba(OH)_2$	2	87	10:1	77[e]

[a] $LiOCH(CF_3)_2/HOCH(CF_3)_2$ (1.24 equiv), *n*-BuLi (1.18 equiv), $(CH_3O)_2POCH_2CO_2CH_3$ (1.20 equiv), DME, 0.24 M in substrate, −14 °C; LiCl, DBU: see ref 2a; $Ba(OH)_2$: see ref 2c. [b] *E*/*Z* ratios reported that exceed 20:1 were determined by HPLC analysis; all others were determined by ^1H NMR analysis (maximal value: >19:1). [c] Isolated yield of the *E*-olefin, unless otherwise noted. [d] HPLC yield, determined using biphenyl as an internal standard. [e] Isolated yield of *E* and *Z* isomers combined.

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(4) For a discussion of the properties of fluorinated alcohols and their use in synthesis, see: Bégué, J.-P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, 18.

(5) Deprotonation of HFI with *n*-butyllithium produces a modest exotherm that is readily controlled under typical laboratory conditions. For example, addition of a solution of *n*-butyllithium in hexanes (2.48 M, 2.28 mL, 5.65 mmol, 1 equiv) via syringe over 6 min to a solution of HFI (0.627 mL, 5.95 mmol, 1.05 equiv) in DME (20 mL) at −14 °C produced a maximum internal temperature of −6.5 °C.

(6) We did encounter some difficulty in reproducing our results from run to run in small-scale experiments using the Masamune–Roush protocol.[2a] This we traced to variations in the concentration of lithium chloride, introduced by errors in weighing small amounts of this hygroscopic reagent. In this regard, the in situ protocol for the generation of LiHFI was found to be both convenient and highly reproducible in small-scale experiments. A similar protocol for the generation of lithium chloride in situ might also be effective, but was not explored.

We investigated the degree to which (adventitious) moisture might influence HWE olefination by the new procedure and found that as much as 5 equiv of water only slightly increased the amount of epimerized product (examining the transformation of entry 1, Table 1) and had little effect on the extent of conversion and *E*-selectivity of the reaction. By contrast, the presence of excess HFI proved to be deleterious by all measures (conversion, degree of epimerization, and *E*-selectivity). This is a distinction from the intramolecular HWE reaction of Scheme 1, where a large excess of TFE (100 equiv) was required for optimum results. It is evident that the intramolecular HWE olefination of Scheme 1 differs considerably from the intermolecular HWE reactions reported here, not only from the varying influences of the respective fluorinated alcohols in the two reactions but also from the much higher reaction temperature required (+80 °C vs −14 °C). Further evidence in this regard is the fact that when substrate **1** was subjected to LiHFI-mediated olefination conditions (CH_3CN, 92 °C), the macrocycles **2** and 18-*epi*-**2** were formed in a ratio of 2.6:1, with poor conversion (16%).[7]

To determine the degree to which trimethyl phosphonoacetate (pK_a ~18−19 in DMSO,[8] ~12 in H_2O[9]) is deprotonated by LiHFI (pK_a HFI = 18.2 in DMSO,[10] 9.3 in H_2O[4]) in DME we conducted a ^{31}P NMR study (Figure 1), much like that conducted by Masamune, Roush, and co-workers in their original report.[2a] The data suggest that the equilibrium between trimethyl phosphonoacetate and its lithium salt using 0.98 equiv of LiHFI as base greatly favors the former species (cf. Figure 1b,c), but the breadth of the ^{31}P resonance in Figure 1c is indicative of rapid exchange under the conditions of the NMR experiment. Thus, we speculate that the primary anionic species in the reaction is LiHFI, and further, that LiHFI does not induce epimerization of the aldehyde substrates we have examined at a rate that is competitive with HWE olefination. It must be the case that lithium trimethyl phosphonoacetate, as formed under the conditions described, also does not induce any appreciable epimerization of the aldehyde substrates examined.

In conclusion, we have found that the exceedingly weak base LiHFI is notably effective in intermolecular HWE olefinations of epimerizable aldehydes. We anticipate that this reagent may be of utility in other base-mediated transformations as well.

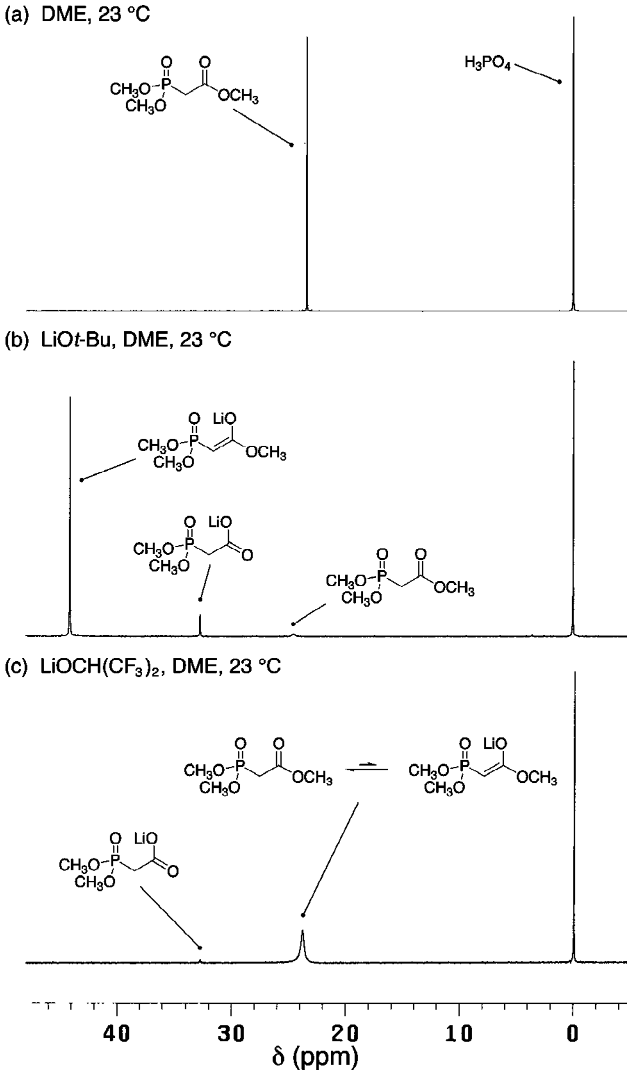

Figure 1. ^{31}P NMR spectra of (a) $(CH_3O)_2POCH_2CO_2CH_3$ in DME at 23 °C, (b) as in (a) plus 1.00 equiv *t*-BuOLi, (c) as in (a) plus 0.98 equiv of $LiOCH(CF_3)_2$. Each spectrum is referenced to an external standard of 85% phosphoric acid in water.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] The reported pK_a of triethyl phosphonoacetate in DMSO is 18.6: Evans, D. A. Evans pK_a Table, http://daecr1.harvard.edu/ (accessed Jul 2005).

[9] The reported pK_a of triethyl phosphonoacetate in water is 11.9: Sokolov, M. P.; Gazizov, I. G.; Mavrin, G. V. *Zh. Obshch. Khim.* **1989**, *59*, 1043.

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