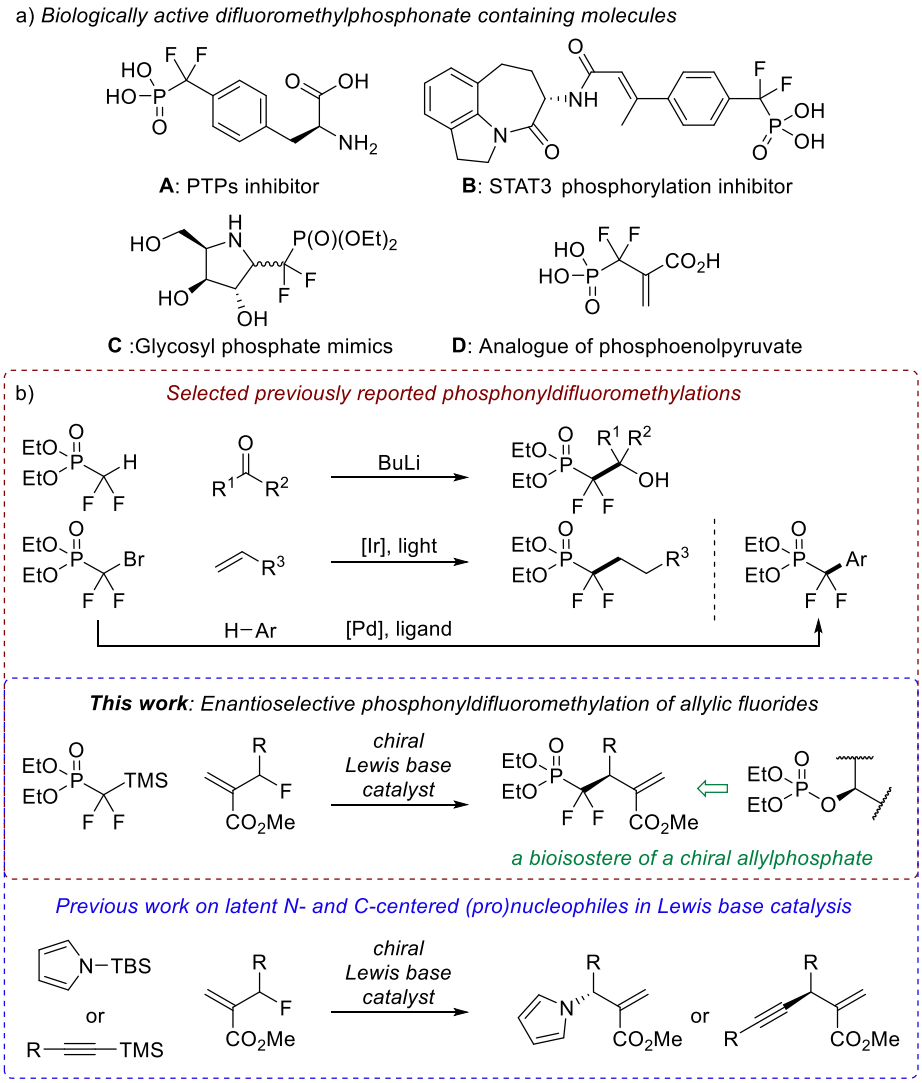
Enantioselective Lewis Base Catalyzed Phosphonyldifluoromethylation of Allylic Fluorides Using C-Silyl Latent Pronucleophile

You Zi, Markus Lange and Ivan Vilotijevic*

Institute of Organic Chemistry and Macromolecular Chemistry, Friedrich Schiller University Jena, Humboldtstr. 10, 07743 Jena, Germany.
E-mail: ivan.vilotijevic@uni-jena.de

Abstract: The first enantioselective phosphonyldifluoromethylation is enabled by the use of diethyl (difluoro(trimethylsilyl)methyl)pho-sphonate reagent as a latent pronuclephile in Lewis base catalyzed substitution of allylic fluorides. The reactions proceed as kinetic resolution to produce both the difluoromethylphosphonate products and the remaining fluorides in good yields and with high stereoselectivity. The use of cinchona based alkaloid catalysts enables the facile synthesis of both enantiomers of the difluoromethylphosphonate products.

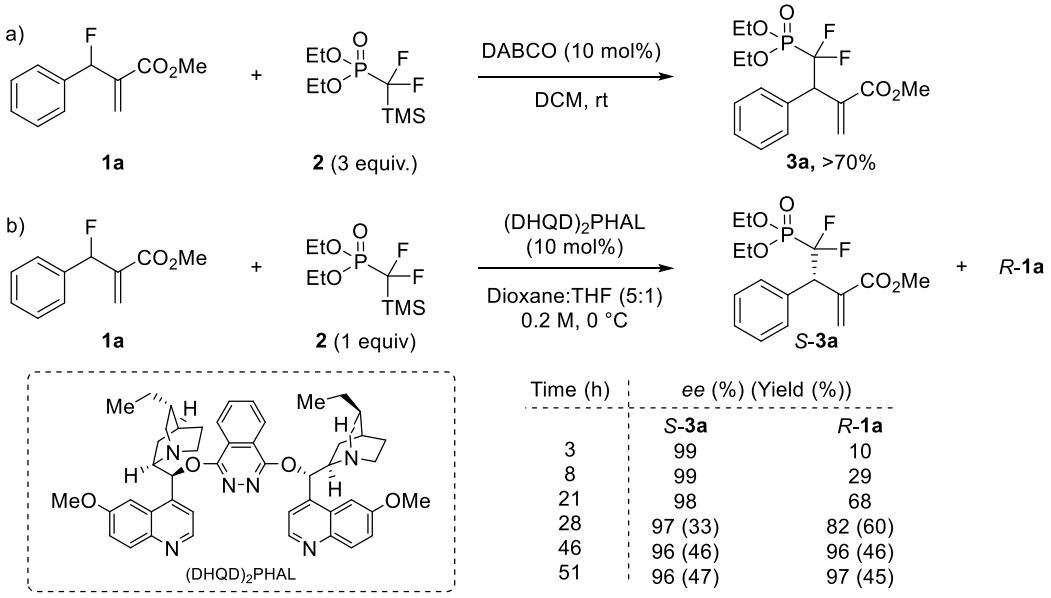
Difluoromethyl group, an oxygen bioisoster and a lipophilic hydrogen-bond donor, is commonly used in medicinal chemistry as a replacement for hydroxyl groups that improves the properties of biologically active molecules.[1] In a similar vein, difluoromethylphosphonate motifs (–$CF_2P(O)(OR)_2$) have emerged as metabolically stable bioisosters of phosphates.[2] They are surprisingly resistant to hydrolysis and therefore bioavailable unlike the typical phosphate analogues. The phosphonic acids mimic the tetrahedral transition state in hydrolysis of peptides which may also be the basis for biological activity of numerous difluoromethylphosphonate containing enzyme inhibitors.[3] Pioneering examples include protein tyrosine phosphatase (PTP) inhibitors (**A**, Scheme 1),[4] STAT3 phosphorylation inhibitors (**B**),[5] mimics of sugar phosphates (**C**)[6] and analogues of phosphoenolpyruvate (**D**).[7] The resulting demand for difluoromethylphosphonates has inspired the development of strategies to introduce this structural motif into drug like molecules (Scheme 1b).[8] These include nucleophilic additions and substitutions with difluoromethylphosphonato anion with suitable electrophiles,[9] additions of the difluoromethylphosphonato radical to π-systems,[10] and the transition metal catalyzed coupling reactions for synthesis of aryldifluoromethylphosphonates.[11] Despite the abundance of naturally occurring chiral organophosphates, the stereoselective methods to prepare difluoromethylpho-sphonates featuring an adjacent stereogenic center are currently limited to substrate controlled diastereoselective reactions.[9c,9g] A catalyst controlled enantioselective method to introduce difluoromethylphosphonates while creating and controlling the configuration of an adjacent stereogenic center would be an enabling factor for further studies of this important bioisostere.[12] With this in mind, we set off to develop a method to produce such chiral bioisosteres of alkyl or allyl phosphates in enantioselective fashion.



Scheme 1 (a) Examples of biologically active difluoromethylphosphonates (b) Comparison of this work with the previous methods for phosphonyldifluoromethylation and the use of latent (pro)nucleophiles in Lewis base catalysis

Allylic substitutions have long served as a powerful tool for stereoselective synthesis both as transition metal and Lewis base catalyzed reactions, the latter considered an important part of the green chemistry toolbox.[13] The most common Lewis base catalyzed allylic substitutions utilize Morita-Baylis-Hillman adducts as electrophiles,[13c,13d] but the scope of these reactions for N- and C-centered nucleophiles is limited.[14] To address these challenges, we introduced the concept of latent nucleophiles, molecules that are not nucleophilic themselves but can be activated to act as nucleophiles in Lewis base catalyzed reactions.[15] C- and N-trialkylsilyl latent (pro)nucleophiles[16] undergo enantioselective Lewis base catalyzed allylation with allylic fluorides (Scheme 1b).[15,17] In these reactions, the formation of the activated nucleophile depends on the decomposition of the silicate intermediate formed by nucleophilic addition of the fluoride to the silyl group of the latent pronucleophiles.[15a,17a,18] We hypothesized that this strategy could be generally applicable to a variety

of stabilized C-nucleophiles and useful in addressing specific synthetic problems. Here, we report that (difluoro(trime-thylsilyl)methyl)phosphonates serve as versatile latent pronucleophiles in Lewis base catalyzed substitutions of allylic fluorides and enable the development of the first enantioselective method to introduce (diethoxyphospho-ryl)difluoromethyl group, while controlling the configuration of the adjacent stereogenic center.



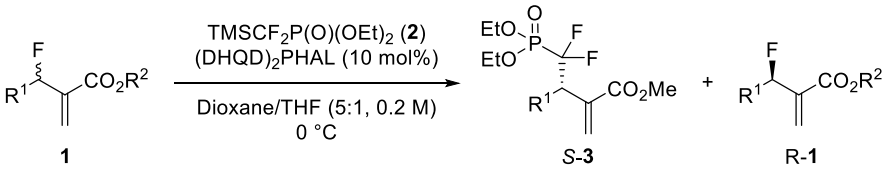
Time (h)	*ee* (%) (Yield (%))	
	S-**3a**	*R*-**1a**
3	99	10
8	99	29
21	98	68
28	97 (33)	82 (60)
46	96 (46)	96 (46)
51	96 (47)	97 (45)

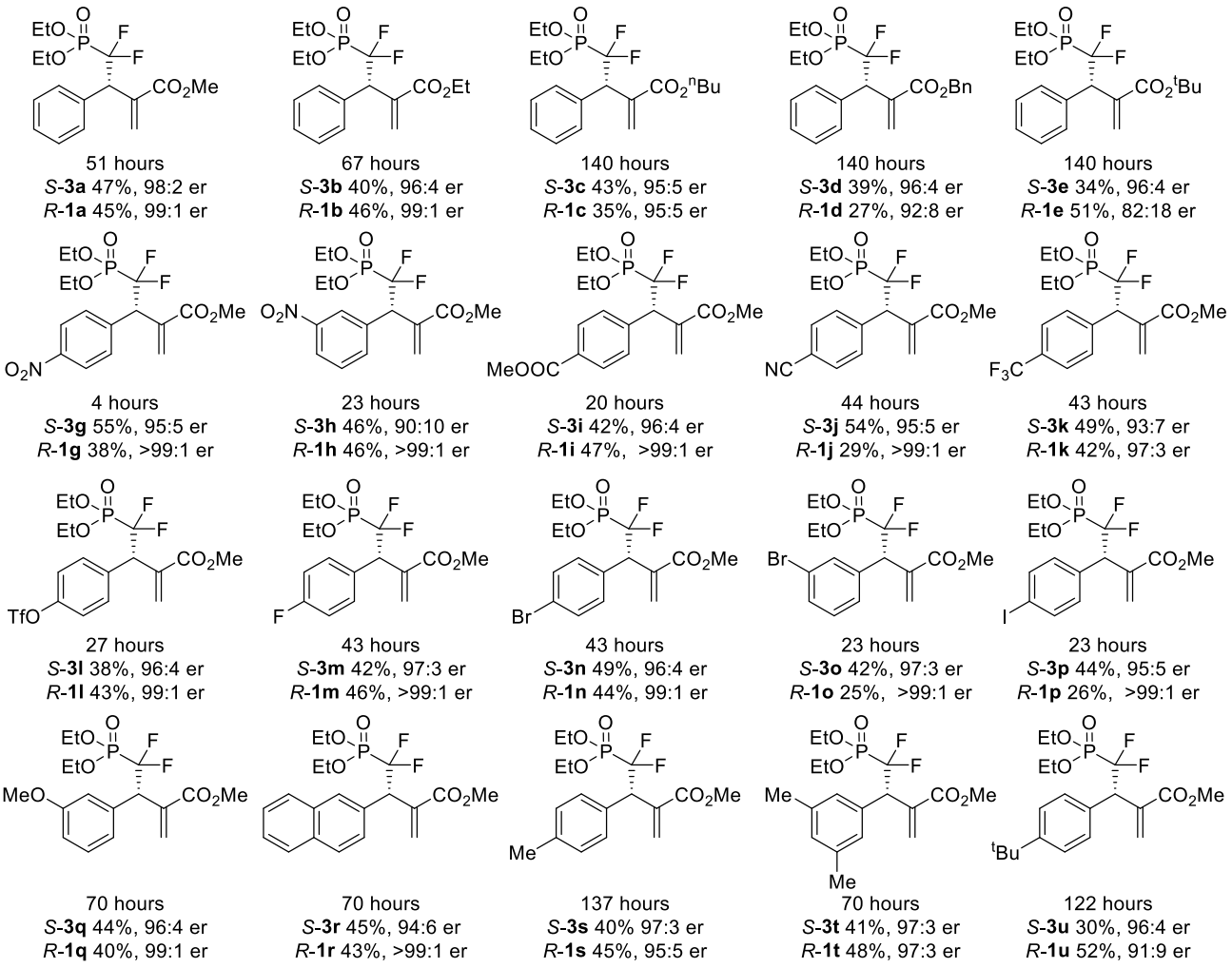
Scheme 2 Early optimization studies and the kinetic resolution of **1a**.

The feasibility of our approach was evaluated using commercially available diethyl (difluoro(trimethylsilyl)methyl)-phosphonate **2** in DABCO catalyzed allylic substitution of allylic fluoride **1a**, derived from the Morita-Baylis-Hillman alcohol adduct of acrylic ester and benzaldehyde (Scheme 2a). Good yields in this reaction were achieved only if excess of the latent pronucleophile **2** was used to increase the conversion of the fluoride to the corresponding (difluoromethyl)phosphonate **3a**. Accordingly, the initial optimization efforts using chiral Lewis base catalysts were made with superstoichiometric quantities of **2**. In the presence of $(DHQD)_2PHAL$ catalyst, most reactions proceeded with good enantioselectivity but, despite the use of excess of the reagent, yields for the desired allylation product remained close to, but below 50%. This was indicative of a kinetic resolution scenario,[17a] where one of the enantiomers of allylic fluoride readily reacts with the chiral catalyst while the other enantiomer remains unchanged.

To reconcile the need for superstoichiometric quantities of the reagent that would increase conversion rates and the requirement for higher concentration of the fluoride that could drive kinetic resolution to completion with respect to the reagent, further optimization studies were focused on reactions using equimolar quantities of allylic fluoride and the reagent (Scheme 2b). The variables in reaction conditions screen included: the identity of chiral catalyst, catalyst loading, reaction solvent, temperature and concentration (for details of optimization studies please see supporting information). In 5:1 mixture of dioxane and THF at 0 °C with 10 mol% $(DHQD)_2PHAL$ catalyst, the reactions of **1a**

and **2** proceeded to close to 50% conversion after 51 hours and afforded the allylation product **3a** in 47% yield and 98:2 ratio of enantiomers (Scheme 2b). Closely monitoring the reaction progress showed that the ratio of enantiomers in product remained nearly constant throughout the reaction, but that of the allylic fluoride steadily increased with time/conversion (Scheme 2b).

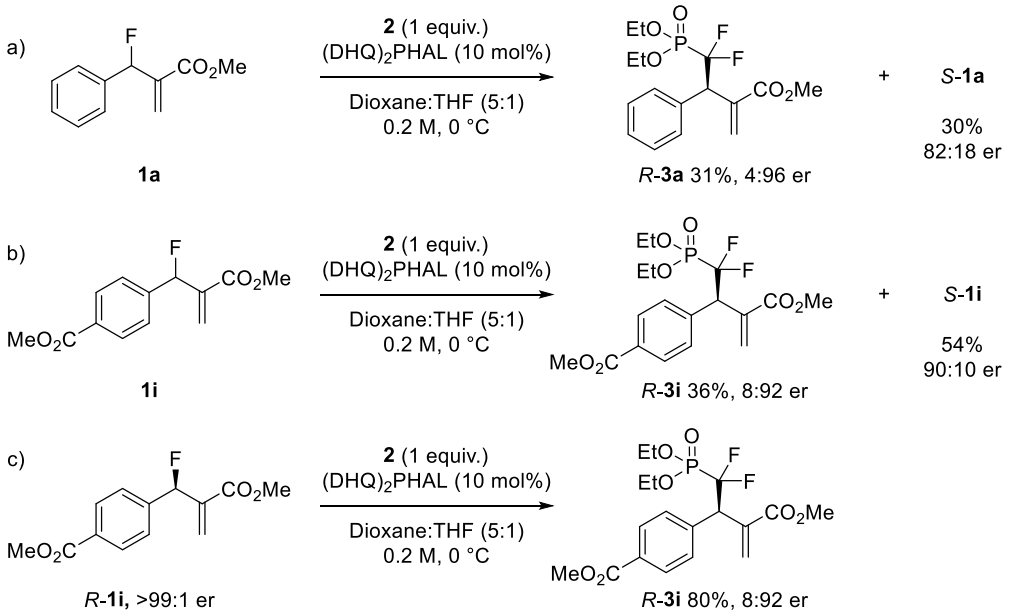




Scheme 3 Enantioselective $(DHQD)_2PHAL$ catalyzed allylic substitution of allylic fluorides **1** using **2** as the latent pronuclephile.

Upon optimization of the reaction conditions, the reaction scope for allylic fluorides was evaluated (Scheme 3). The low reaction rates allowed for close monitoring of the kinetic resolution reactions by NMR and/or HPLC on chiral stationary phase. The reactions were allowed to run until there were no further changes in the er of the remaining allylic fluoride or when it reached the level

equal or higher than 99:1. A range of esters, including methyl, ethyl, *n*-butyl, benzyl and *t*-butyl esters (**1a**-**1e**), were investigated and converted to the corresponding products *S*-**3a**-**3e** in good yields (34-47%) with good enantioselectivity (95:5 to 98:2 er). The presence of electron withdrawing groups in allylic fluorides **1g**-**1l** noticeably increased the reaction rates and the (difluoromethyl)phosphonate products *S*-**3g**-**3l** were isolated in both good yields (38-55%) and enantioselectivities (90:10 to 96:4 er). Allylic fluorides featuring halogen substituents **1m**-**1p**, were also well tolerated under the optimal conditions, and all gave the products *S*-**3m**-**3p** in good yields (42-49%,) with excellent degrees of stereocontrol (95:5 to 97:3 er). The reactions with allylic fluorides bearing electron rich aromatic substituents **1q**-**1u** were subsequently carried out. These uniformly required longer time to reach half-conversion but ultimately led to satisfactory outcomes with yields between 30% and 45% and enantiomeric ratios between 94:6 and 97:3. Installing alkyl instead of aryl substituents lowered the reaction rates to synthetically impractical level (**3f**). In most reactions, the enantiomeric ratio for the remaining ally fluorides *R*-**1** was 99:1 er or higher. Absolute configuration of the products was assigned by analogy to similar reactions using $(DHQD)_2PHAL$.

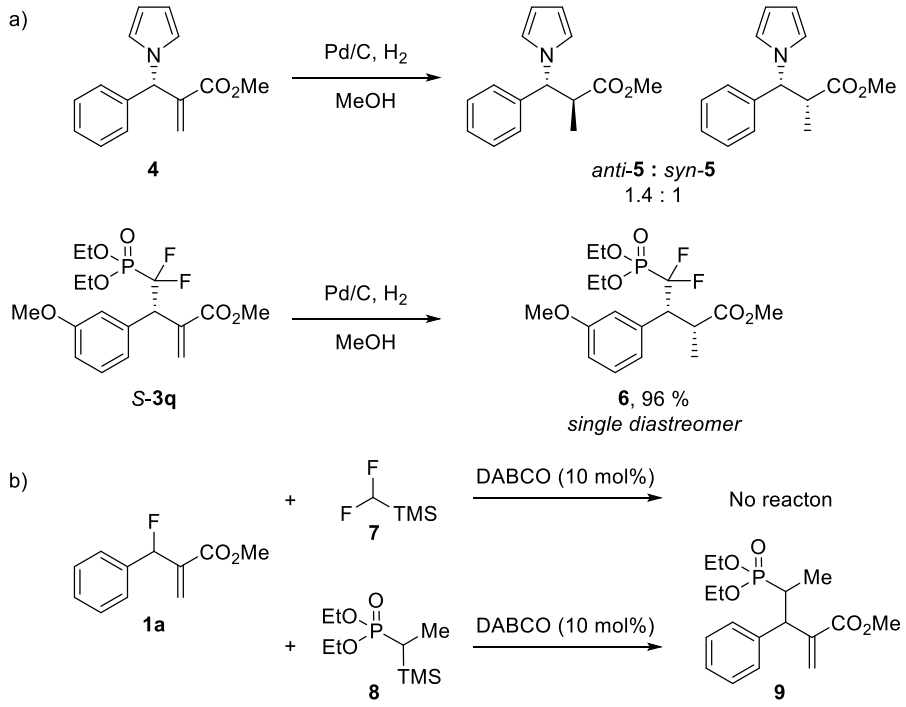


Scheme 4 Comparative test with $(DHQ)_2PHAL$ instead of $(DHQD)_2PHAL$ and reaction with enantioenriched allylic fluoride.

Switching the catalyst to $(DHQD)_2PHAL$ pseudoenantiomer, $(DHQ)_2PHAL$, unsurprisingly resulted in the preferential formation of the other enantiomer although with slightly lower stereoselectivity (4:96 er for *R*-**3a** and 8:92 for *R*-**3i**, unoptimized results, Scheme 4). Furthermore, the enantioenriched allylic fluoride *R*-**1i** (>99:1 er) recovered from the $(DHQD)_2PHAL$ catalyzed reactions could be used as a starting material to produce *R*-**3i** with same stereoselectivity and in 80% yield in the presence of $(DHQ)_2PHAL$.

In addition to serving as a bioisostere of phosphates, difluoromethylphosphonate strongly influences conformational preferences of the product which can be exploited to control

stereoselectivity in subsequent transformation. For example, simple hydrogenation of analogues containing N-heterocycles instead of the difluoromethylphosphonate proceeds with low diastereoselectivity (1.4:1)[15b] while the same reactions of difluoromethylphosphonate analogues afford only the *syn* diastereomer of **6** in nearly quantitative yield of 96% (Scheme 5a).



Scheme 5 Diastereoselective hydrogenation of *S*-**3q** and influences of the difluoromethylphosphonate on stereochemical outcome. Attempted reactions of **1a** with related latent pronucleophiles.

The effects of the fluorine atoms and the phosphonate on the stability of the activated nucleophile were briefly explored by examining the DABCO-catalyzed reactions of allylic fluoride **1a** with the related latent pronucleophiles: TMS-difluoromethane **7** and the diethyl (1-(trimethylsilyl)ethyl)pho-sphonate **8** (Scheme 5b). **7** failed to react with the allylic fluoride while the phosphonate containing alkylsilane **8** afforded the desired product **9** although in low yields (unoptimized results). This indicates that the formation and decomposition of the silicate intermediate may be the determining factor for the outcome of the reaction.

In conclusion, the first enantioselective method to introduce a phosphate bioisostere, -$CF_2P(O)(OR)_2$, has been developed by using diethyl (difluoro(trimethylsilyl)me-thyl)phosphonate reagent **2** as a latent pronucleophile in Lewis base catalyzed substitution of allylic fluorides. The reactions proceed as kinetic resolution of the racemic fluorides which affords both the difluoromethylphosphonate product and the recovered allylic fluoride in good yields and with high enantiomeric ratios. The reactions are operationally simple, use commercially available reagent and catalysts and transform readily available Morita-Baylis-Hillman fluorides to the stable difluoromethylphosphonates. Both enantiomers of the product can be readily accessed and they are

amenable to further stereoselective transformations owing to the conformational effects of the difluoromethylphosphonate.

Acknowledgements

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16. We use the term latent nucleophile for N-silyl compounds because the silyl group attenuates the nucleophilicity of the otherwise nucleophilic N-H analogue. For C-centered nucleophile,

the preferred term is latent pronucleophile because both the C-silyl compound and the C-H analogue are normally not nucleophilic (latent) and are therefore only *pro*nucleophiles.

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18. With multiple ligands on silicon of the proposed silicate complex, the decomposition of the silicate should produce the most stable anion/weakest base. For N-trialkylsilyl latent nucleophiles, this is always the N-centered anion by virtue of all N-H compounds being more acidic than the corresponding alkanes. The same strategy applied to C-trialkylsilyl latent ponucleophiles, requires the stabilized carbon nucleophile to be produced to avoid selectivity issues (stabilized C-nucleophile vs. alkyl nucleophile). Shibata has shown that CF_3 and alkynyl nucleophiles can be introduced via this strategy.

Graphical Abstract