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Synthesis of (Difluoromethyl)cycloalkenes from 2-Cycloalkenones by Utilizing Phospha-Brook Rearrangement

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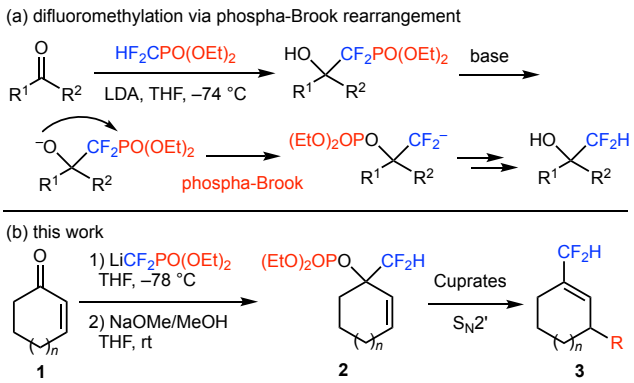
Abstract. Difluoromethyl-substituted allylic phosphates were synthesized from 2-cycloalkenones through the addition of a (difluoromethyl)phosphonate and subsequent phospha-Brook rearrangement. The obtained allylic phosphates were converted to the corresponding difluoromethyl-substituted cycloalkenes using the Cu-mediated S_N2' reaction of Grignard or organolithium reagents.

Keywords: Fluorine; Phosphorus; Copper; Cycloalkenone; (Difluoromethyl)alkene

The introduction of fluorinated groups to bioactive molecules is a promising strategy to achieve a suitable drug lead compounds in the modern pharmaceutical industry,[1] because these groups have considerable impacts on various characteristics of organic molecules, such as acidity, hydrogen-bonding interactions, lipophilicity, and so on.[2] The difluoromethyl (CF_2H) group is one of the most fascinating fluorinated groups because it functions as a hydrogen-bond donor.[3] As a result of this property, the CF_2H group can be employed as a lipophilic bioisostere for hydroxy (OH) and mercapto (SH) groups.[4] Owing to the importance of the CF_2H group, enormous efforts have been devoted toward the identification of efficient methods for the synthesis of biologically interesting molecules bearing this moiety.[5]

We became interested in difluoromethylated alkenes because they can be considered as surrogates of enol tautomers of ketones and aldehydes. Despite advances in difluoromethylation methodology, the synthesis of difluoromethylated alkenes remains a major challenge in synthetic organic chemistry.[6] The syntheses of (difluoromethyl)cycloalkenes have been underdeveloped and thus, the scope was almost limited to acyclic compounds.[7] 1-(Difluoromethyl)cyclohexene was previously obtained by the reaction of cyclohexenecarbaldehyde with SF_4; however, the yield was moderate.[8] Recently, transition-metal-mediated difluoromethylation of cycloalkenyl electrophiles has been disclosed, but this method still have disadvantages such as the use of expensive precious metal catalyst and the *N*-heterocyclic carbene Ag complex as the difluoromethyl anion source.[9]

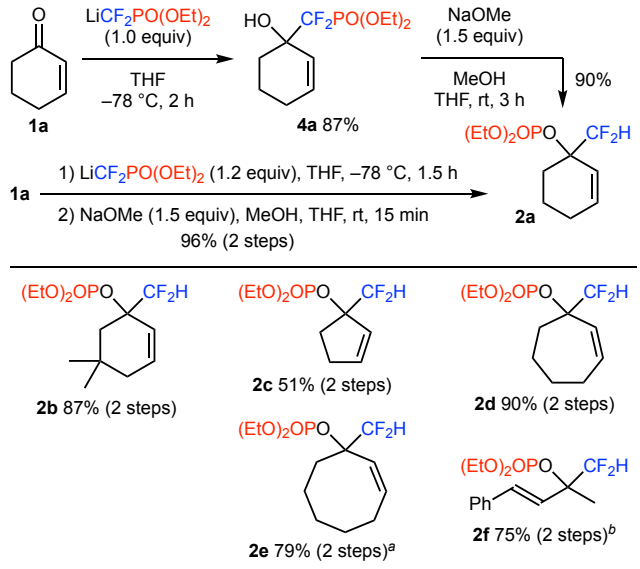
In this regard, a new synthetic method utilizing an inexpensive difluoromethyl surrogate and readily accessible substrates would be highly desirable. We focused on diethyl (difluoromethyl)phosphonate as the difluoromethyl surrogate because its acidic proton can be abstracted by lithium diisopropylamide (LDA) and the generated anion adds to ketones and aldehydes efficiently.[10] Moreover, treatment of the obtained adduct with a base produces difluoromethylated carbinols through the C-to-O phospha-Brook rearrangement (Scheme 1a).[10a] If this method were applied to cycloalkenones **1**, allylic phosphates **2** would be obtained (Scheme 1b). Nevertheless, the expected difluoromethylated cyclic phosphates have not been utilized for further C–C bond formations,[11] even though allylic phosphates are useful intermediates in organic synthesis. Therefore, we investigated the synthesis of difluoromethylated allylic phosphates **2** and their S_N2' reaction with organocuprates. This two-step synthesis of 3-substituted 1-(difluoromethyl)cycloalk-1-enes **3** is remarkable as an unprecedented deoxygenative difluoromethylation of cycloalkenones.



Scheme 1. (a) Previous difluoromethylation of ketones and aldehydes using diethyl (difluoromethyl)phosphonate and

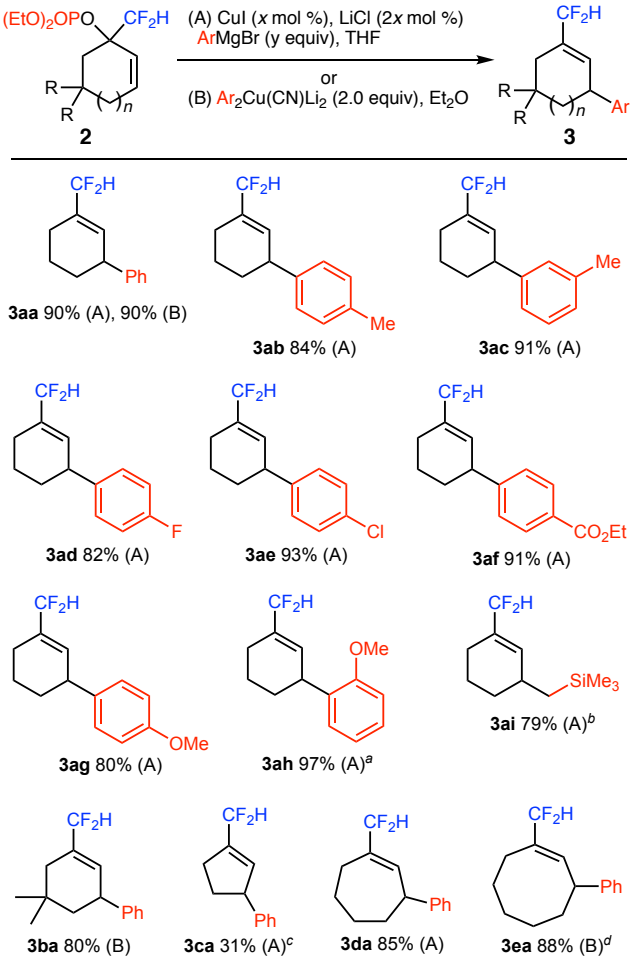
(b) two-step synthesis of difluoromethylcycloalkenes through a phospha-Brook rearrangement.

At the outset, addition of the (difluoromethyl)phosphonate anion to cycloalkenones was investigated (Scheme 2). After deprotonation with LDA, the resultant (difluoromethyl)phosphonate anion reacted with cyclohexenone (**1a**) at –78 °C for 2 h to afford allylic alcohol **4a** in 87% yield. Subsequently, **4a** underwent phospha-Brook rearrangement upon treatment with NaOMe/MeOH in THF at room temperature for 3 h. After purification with silica gel chromatography, the desired allylic phosphate **2a** was obtained in 90% yield. TLC analysis of the reaction progress revealed that the phospha-Brook rearrangement was complete within 15 min. Thus, crude **4a** was directly treated with NaOMe/MeOH for 15 min to afford **2a** in 96% yield over the two steps from **1a**. Similarly, 5,5-dimethylcyclohexenone (**1b**), cyclopentenone (**1c**), cycloheptenone (**1d**), and cyclooctenone (**1e**) could be used for the two-step transformation, affording the corresponding products **2b**–**2e** in 51–90% yields. The lower yield of **2c** was ascribed to partial dephosphonylation during chromatographic purification; the phospha-Brook rearrangement of the isolated phosphonate **4c** proceeded quantitatively, as indicated by ^{1}H NMR analysis of the crude material. Although small amounts of **1e** remained even after prolonged reaction with the (difluoromethyl)phosphonate anion (3.5 h), the subsequent phospha-Brook rearrangement afforded **2e** in 79% yield. Allylic phosphate **2f** was obtained from acyclic enone **1f** in 75% yield when NaH was used as the base instead of NaOMe for the phospha-Brook rearrangement.



Scheme 2. Synthesis of difluoromethyl-substituted allylic phosphates **2a**–**f** from α,β-unsaturated ketones **1a**–**f**. [a]The first step was performed for 3.5 h. [b]NaH was used instead of NaOMe.

Having accomplished the synthesis of difluoromethyl-substituted allylic phosphates, the copper-catalyzed reaction of phosphate **2a** with a Grignard reagent was investigated, according to the previous report (Scheme 3).[12] After optimization of the reaction conditions (Table S1, Supporting Information), the reaction of **2a** with PhMgBr (4.0 equiv) was performed in the presence of 10 mol % CuI and 20 mol % LiCl in THF at –78 °C for 2 h, affording **3aa** in 90% isolated yield. Other catalysts, such as Fe(acac)$_3$ (acac: acetylacetonate) and NiBr$_2$, were completely ineffective. Alternatively, the reaction of **2a** with a higher-order cyano cuprate, Ph$_2$Cu(CN)Li$_2$ (2 equiv), in Et$_2$O at –78 °C for 1.5 h afforded **3aa** in 90% yield (Scheme S1, Supporting Information).

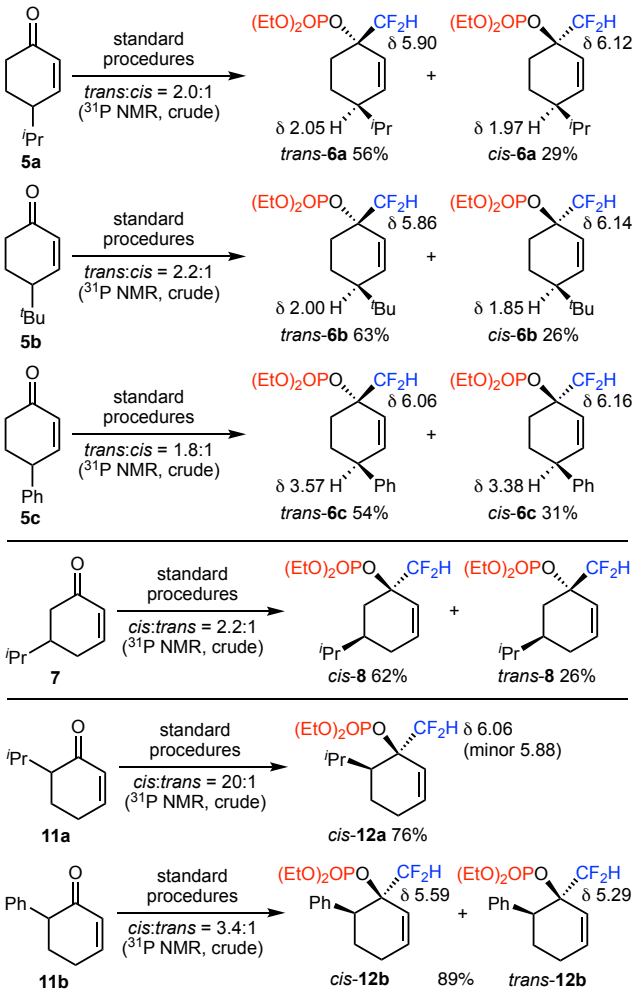


Scheme 3. Scope of S$_N$2' reaction of phosphates **2a**–**e**. Standard conditions: (A) Grignard reagent (4.0 equiv), CuI (10 mol %), LiCl (20 mol %), THF, –78 °C, 2 h; (B) Ph$_2$Cu(CN)Li$_2$ (2 equiv), Et$_2$O, –78 °C, 1.5 h. [a]–30 °C. [b]0 °C. [c]PhMgBr (2.0 equiv), 1 h. [d]–30 °C, 1 h, then 0 °C, 1 h.

The scope of the Cu-catalyzed S$_N$2' reaction was demonstrated by the reactions of **2a** with various Grignard reagents (Scheme 3). The desired products **3ab**–**3ae**, bearing methyl, fluoro, and chloro substituents, were obtained in 82–93% yields. Both

electron-withdrawing and electron-donating groups were tolerated as **3af**–**3ah** were obtained in high yields. In addition to products with *para*-substituted aryl groups, *ortho* and *meta* substituents were also tolerated: **3ac** and **3ah** were obtained in high yields, although the less reactive *o*-methoxyphenyl Grignard reagent required an elevated reaction temperature (–30 °C). Alkyl Grignard reagents could also be used for this method, although we encountered an isolation problem associated with the high volatility of products bearing a simple alkyl group and inseparable side products formed through homocoupling of the Grignard reagents. Nevertheless, **3ai** was successfully obtained in 79% yield using the (trimethylsilyl)methyl Grignard reagent at 0 °C. Because five-membered phosphate **2c** is unstable toward chromatography, the isolated phosphonate **4c** was subjected to the phospha-Brook rearrangement conditions and crude **2c** was then used directly for the subsequent S_N2' reaction. Consequently, **3ca** was obtained, albeit in a much lower yield (31%). Seven-membered phosphate **2d** was efficiently converted to the corresponding S_N2' product **3da** in 85% yield. Although *gem*-dimethylcyclohexene derivative **2b** was found to be unreactive under catalytic conditions A, **3ba** could be obtained in a high yield using the higher order cuprate (conditions B). Similarly, cyclooctene derivative **3ea** was obtained in 88% yield using the higher order cuprate at elevated temperatures (–30~0 °C). In striking contrast to the cyclic phosphates, acyclic phosphate **2f** decomposed under the conditions A.

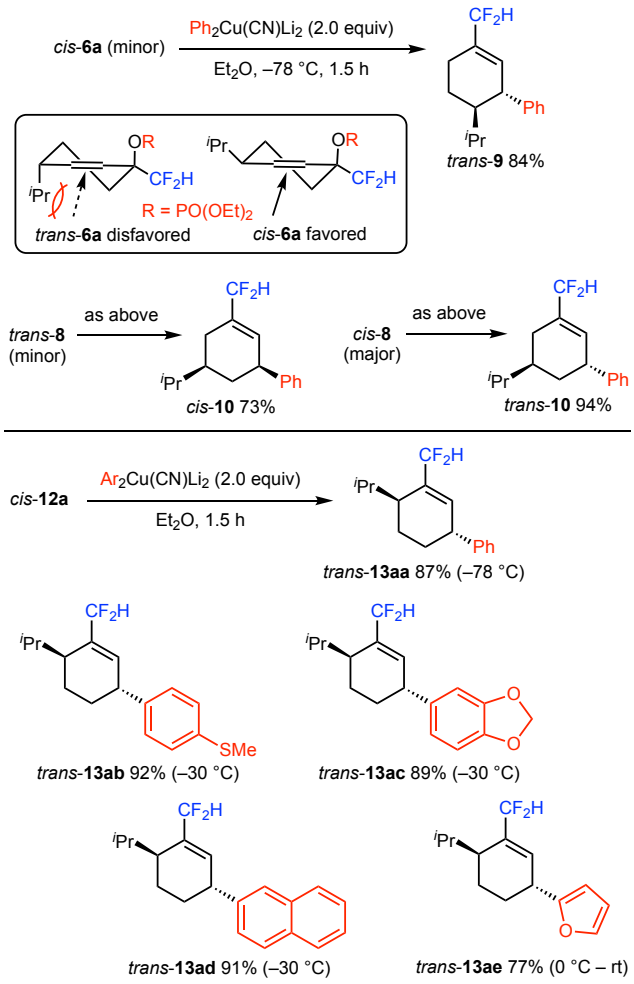
Next, the stereoselectivity in the phosphate synthesis was investigated (Scheme 4). The addition of the phosphonate anion to 4-isopropylcyclohexenone (**5a**) was followed by the phospha-Brook rearrangement to produce a diastereomeric mixture of phosphates **6a**. ^{31}P NMR analysis of the crude product mixture showed that the *trans*/*cis* ratio is 2.0:1. In accordance with this analysis, chromatographic purification afforded *trans*-**6a** and *cis*-**6a** in 56% and 29% yields, respectively. Similarly, *tert*-butyl- and phenyl-substituted derivatives **6b** and **6c** were obtained with *trans*/*cis* ratios of 2.2:1 and 1.8:1, respectively. The relative configurations of **6a**–**c** were determined as follows: *trans*- and *cis*-**6b** were converted to the known alcohols *trans*- and *cis*-**S2**, respectively, and their NMR data were in good agreement with those previously reported (Scheme S2, Supporting Information). The relative configurations of *trans*/*cis*-**6a** and *trans*/*cis*-**6c** were also determined by comparison of their spectral data with those of *trans*/*cis*-**6b**. The observed diastereoselectivity can be explained by axial attack of phosphonate anions to 4-substituted cyclohexenones **5**, similar to the axial attack of acetonitrile anions previously reported.[13] However, the diastereoselectivity observed in this study (ca. 2:1) is much lower than that observed for the addition of $LiCH_2CN$ to **5b** (23:1). This diminished stereoselectivity can be ascribed to the bulkiness of $LiCF_2PO(OEt)_2$, which exerts steric repulsion with the axial proton on C5 (Figue S1, Supporting Information).



Scheme 4. Synthesis of difluoromethyl-substituted allylic phosphates **6a–c**, **8**, and **12a**,**b**.

In the same manner, 5-isopropylcyclohexenone (**7**) was transformed to the corresponding allylic phosphates *trans*/*cis*-**8** with a crude *cis*/*trans* ratio of 2.2:1. Allylic phosphate **12a** was also obtained from 6-isopropylcyclohexenone (**11a**), albeit in a slightly lower yield (76%). Notably, *cis*-**12a** was produced with a high diastereoselectivity (20:1), even though *trans*-**12a** was expected to be the major diastereomer according to the axial addition model (see below). This result can be explained as follows: $LiCF_2PO(OEt)_2$ is considered to be a bulky nucleophile, as evidenced by the modest diastereoselectivity observed for its addition to 4- and 5-substituted cyclohexenones. Thus, the steric repulsion between the phosphonate anion and the bulky isopropyl substituent adjacent to the carbonyl group in **11a** caused high *cis* selectivity (Figue S1, Supporting Information). However, the reaction of **11b** bearing a less bulky phenyl substituent afforded *trans*/*cis*-**12b** in 89% yield as an inseparable mixture with a modest diastereoselectivity of *cis*/*trans* = 3.4:1.

The isolated *trans*- and *cis*-**6a** were separately subjected to an S_N2' reaction (Scheme 5). Because the catalytic method (conditions A) was found to be inefficient, the higher order cuprate, $Ph_2Cu(CN)Li_2$, was used (conditions B). It is widely accepted that the S_N2' reaction of cyclic allyl phosphates with organocuprates proceeds in a stereospecific manner: the newly introduced substituent comes from the opposite face to the phosphate leaving group.[14] In good accordance with this general trend, the minor isomer *cis*-**6a** was efficiently converted to the expected *trans*-**9** in 84% yield. In contrast, *cis*-**9** could not be obtained from the major isomer *trans*-**6a** because the *anti* approach is severely hindered by the adjacent isopropyl substituent. Thus, the control of stereoselectivity in the first addition step is of prime importance for the subsequent transformation of the allylic phosphate intermediates. Similarly, *trans*- and *cis*-**8** were subjected to the S_N2' reaction. Although the expected *cis*-**10** was obtained from *trans*-**8** in a modest yield (73%) due to the formation of unidentified byproduct(s), the reaction of *cis*-**8** uneventfully afforded *trans*-**10** in 94% yield.



Scheme 5. S_N2' reaction of phosphates **6a**, **8**, and **12a** with $Ar_2Cu(CN)Li_2$.

Finally, the S_N2' reaction of *cis*-**12a** with several higher order cuprates was investigated (Scheme 5). The use of $Ph_2Cu(CN)Li_2$ resulted in the formation of the desired product *trans*-**13aa** in 87% yield. Similarly, *p*-(methylthio)phenyl, benzo[d][1,3]dioxol-5-yl, and 2-naphthyl groups were successfully introduced by reactions performed at –30 °C to afford *trans*-**13ab**–**13ad** in high yields. Subsequently, *trans*-**13ab** was transformed to the corresponding sulfone *trans*-**S3** (Scheme S3, Supporting Information), which was unambiguously characterized by X-ray analysis.[15] In contrast, $(2\text{-furyl})_2Cu(CN)Li_2$ was found to be much less reactive. Thus, its reaction was conducted at higher temperatures (0 °C to room temperature), and the desired product *trans*-**13ae** was obtained in 77% yield.

In conclusion, we have demonstrated that addition of the lithium anion of diethyl (difluoromethyl)phosphonate to 2-cyclohexenones produced the corresponding 1,2-addition products, which were subsequently treated with NaOMe/MeOH to induce the phospha-Brook rearrangement. As a result, difluoromethyl-substituted allylic phosphates were obtained in 51–96% yields. Moreover, the Cu-mediated reactions of the obtained allylic phosphates with Grignard or aryllithium reagents regioselectively afforded the expected S_N2' products. This new method of synthesizing difluoromethyl-substituted cycloalkenes is intriguing as an unprecedented deoxygenative 1,3-difunctionalization of 2-cycloalkenones.

Experimental Section

Synthesis of 1-(difluoromethyl)cyclohex-2-en-1-yl diethyl phosphate (2a). To a solution of **4a** (568.4 mg, 2 mmol) in THF (20 mL) was added NaOMe (164.0 mg, 3 mmol) in MeOH (0.75 mL) at ambient temperature. After stirring at ambient temperature for 3 hours, the reaction was quenched by adding sat. aq. NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (3×10 mL). The combined organic extract was washed with brine (5 mL), and dried over anhydrous Na_2SO_4. The solvents were evaporated *in vacuo*, and the obtained crude product was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to afford **2a** (509.8 mg, 90%) as a colorless oil.

Synthesis of (3-(difluoromethyl)cyclohex-2-enyl)benzene (3aa). In a round-bottom flask, CuI (5.6 mg, 0.03 mmol) and LiCl (3.0 mg, 0.06 mmol) were heated at 140 °C under vacuum for 3 h. After cooling to room temperature, to the above dried catalyst was added dry THF (2 mL) and a solution of allylic phosphate **2a** (85.5 mg, 0.30 mmol) in THF (2 mL). To the resultant solution was added dropwise a solution of PhMgBr (3 M in Et_2O, 400 µL, 1.2 mmol) in dry THF (4 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 2 hours. The reaction was quenched by adding sat. aq. NH_4Cl (5 mL), and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic extract was washed with brine (5 mL), and dried over anhydrous Na_2SO_4. The solvents were evaporated *in vacuo,* and the obtained crude product was purified by silica gel column chromatography (hexane) to afford **3aa** (56.6 mg, 90%) as a colorless oil.

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[15] CCDC-1904124 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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