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Phosphorus(III)-Mediated, Tandem Deoxygenative Geminal Chlorofluorination of 1,2-Diketones

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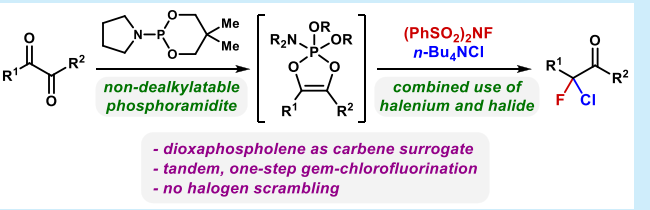
ABSTRACT: Tetrasubstituted carbon containing two different halogen substituents was constructed in a single-step operation by utilizing the carbene-like reactivity of dioxaphospholene through the tandem reaction of electrophilic and nucleophilic halogenating reagents. It was crucial to devise non-dealkylatable phosphoramidite, which enabled the efficient formation of geminal chlorofluorides from various 1,2-diketones with $(PhSO_2)_2NF$ and *n*-Bu_4NCl. In addition, selective functionalization of the chlorine substituent was demonstrated, and the absence of halogen scrambling was confirmed.



The simultaneous introduction of two halogen substituents onto organic molecules is generally accomplished via vicinal dihalogenation of unsaturated functional groups, which is one of the most extensively studied fundamental transformations in organic chemistry.[1] The scope of such reaction has expanded greatly in recent years to culminate in the development of enantioselective dihalogenation[2a−d] and interhalogenation[2e] as well as stereochemically complementary *syn*-dihalogenations.[3] In contrast, geminal dihalogenation at one carbon center has received much less attention probably because such reactions usually do not involve interesting selectivity issues. However, if the two halogen substituents are different, it would lead to the construction of an unusual tetrasubstituted stereocenter such as the chlorofluorinated carbon in **1** (Figure 1A). This kind of geminal interhalide has high synthetic utility.[4,5] For example, **1** can be transformed into a range of fluorinated organic molecules (**2**) typically via S_N2 displacement of the more reactive chlorine substituent as demonstrated by the groups of Yamamoto and Shibatomi.[4b,c] Geminal chlorofluoride has been synthesized most successfully via sequential electrophilic halogenations of an activated methylene such as 1,3-dicarbonyl compounds (**3**) (Figure 1B).[4] However, because this process employs the same kind of reactivity twice, it has to be a two-step operation. If the two electrophilic reagents are present together, the starting material will not be able to distinguish them. Moreover, it is often difficult to avoid double incorporation of the same halogen, and the resulting overhalogenated side product such as **5** is very difficult to separate from the desired product **4**.[4a]

To solve these problems, the two halogenating reagents must have different, distinguishable reactivities. Thus, it can be postulated that the combined use of an electrophilic halenium and a nucleophilic halide would allow the development of a tandem, one-step geminal interhalogenation (Figure 1C). To perform such a transformation, the reactant must be both

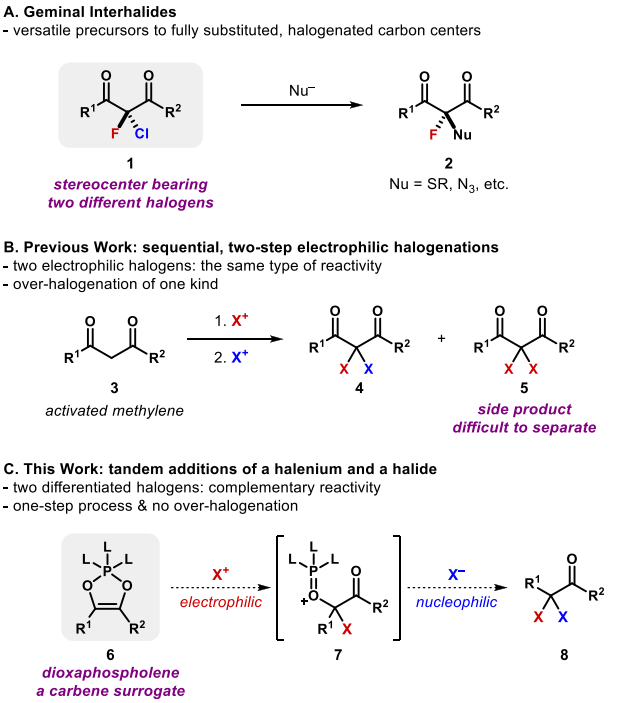


Figure 1. Geminal interhalogenation.

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electrophilic and nucleophilic at the same carbon. This kind of ambivalent reactivity is a characteristic of carbene. In recent years, dioxaphospholene (**6**), also known as the Kukhtin–Ramirez adduct, which can be conveniently derived from a 1,2-dicarbonyl compound, has received attention as a highly useful carbene surrogate that can react with an electrophile and a nucleophile in a sequential manner.[6,7] The addition of an electrophile onto **6** leads to the formation of an oxaphosphonium species **7**, which has an excellent leaving group that can be easily displaced by a nucleophile to give the geminally difunctionalized product **8**. Here, we report a tandem, one-step geminal chlorofluorination of 1,2-diketone with a halenium and a halide by taking advantage of the carbene-like reactivity of dioxaphospholene.

Because of the nucleophilic reactivity of the P(III) reagent, the scope of a compatible electrophile in the Kukhtin–Ramirez reaction is rather limited. In our case, the P(III) nucleophile and the halogen electrophile will be consumed together in an unproductive way by forming a halophosphonium adduct unless the complete formation of dioxaphospholene is ensured prior to the addition of a halenium reagent. A brief survey of the P(III) reagent revealed that trialkyl phosphite is capable of facile and complete production of dioxaphospholene with 1,2-diketone.[8] For example, the reaction of triethyl phosphite and benzil afforded dioxaphospholene **6a** quantitatively (Figure 2A). However, the subsequent halogenation was accompanied

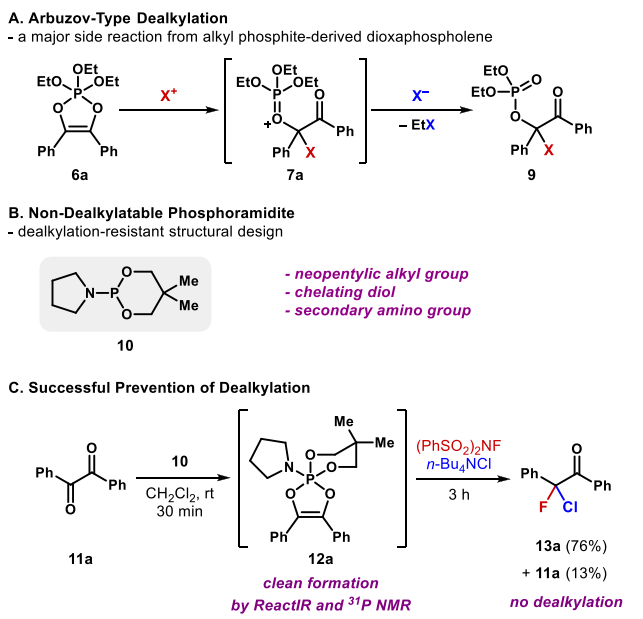
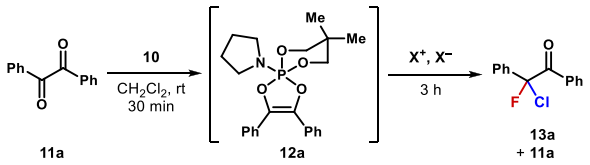


Figure 2. Design of the phosphorus(III) reagent.

by a serious side reaction. Instead of the desired S_N2 displacement at the activated α-carbon, a nucleophilic dealkylation took place at the alkoxy group of phosphite to give phosphate **9**, and no geminal chlorofluoride was obtained. Thus, it turned out that two S_N2 reactions are competing in intermediate **7a**. To facilitate the desired S_N2 reaction at the α-carbon, the steric hindrance around this center must be alleviated by employing a small electrophilic halogen, i.e., F^+. In addition, to suppress the undesired dealkylation, we came up with a neopentyl glycol-derived P(III) reagent **10** that should be resistant to nucleophilic displacement (Figure 2B). The bidentate nature of the diol moiety will also increase the kinetic stability of the two P–O bonds. The remaining site is occupied by a secondary amino group, which is also difficult to dealkylate. This newly designed P(III) reagent can be readily prepared in one step from a commercially available chlorophosphite. With **10**, the reaction of benzil (**11a**) produced the dioxaphospholene adduct **12a** cleanly as observed by ReactIR and ^{31}P NMR spectroscopy. Gratifyingly, the subsequent treatment with a fluorenium [$(PhSO_2)_2NF$, NFSI] and a soluble chloride (n-Bu_4NCl) afforded the geminal chlorofluoride **13a** in 76% yield without any detectable sign of dealkylation (Figure 2C). A small portion of the dioxaphospholene **12a** reverted back to the starting material **11a**, which accounted for the mass balance. In addition, no reaction was observed between **12a** and n-Bu_4NCl. Thus, the chlorofluorination is clearly initiated by the electrophilic fluorination.

Encouraged by this promising preliminary result, we evaluated several combinations of other halogenating reagents prior to the substrate survey (Table 1). In contrast to the fairly

Table 1. Survey of Halogenating Reagents[a]



entry	X^+	X^-	**13a** (%)[b]	**11a** (%)[b]
1	$(PhSO_2)_2NF$	n-Bu_4NCl	78	13
2	Selectfluor	n-Bu_4NCl	3	26
3	$(PhSO_2)_2NF$	LiCl	15	45
4[c]	$(PhSO_2)_2NF$	n-Bu_4NCl	26	39
5[d]	$(PhSO_2)_2NF$	n-Bu_4NCl	0	0
6	NCS	n-Bu_4NF	0	11
7	PhthN-Cl	n-Bu_4NF	2	18

[a]Reaction conditions: **11a** (1.0 mmol), **10** (1.0 mmol), X^+ (1.2 mmol), and X^- (1.2 mmol) in CH_2Cl_2 (6.0 mL). [b]Isolated yields after column chromatography. [c]With 2 equiv of **10**. [d]With 4 equiv of **10**.

clean reaction with NFSI (entry 1), the use of another popular electrophilic fluorinating reagent, Selectfluor, afforded a complex mixture (entry 2). The mass balance was poor, and only a trace amount of the desired product **13a** was isolated. Interestingly, when poorly soluble LiCl was employed, a substantial amount of starting material was regenerated (entry 3). Because the displacement with Cl^- is slow, a large portion of fluorooxyphosphonium intermediate must have remained unreacted and then been hydrolyzed to 1,2-diketone upon aqueous workup. The use of an excess amount of **10** was not beneficial. With 2 equiv of **10**, product formation was significantly attenuated (entry 4). Furthermore, the halogenation was completely suppressed when 4 equiv of **10** was employed (entry 5), and dioxaphospholene **12a** remained as a major component in the crude mixture. As mentioned above, the excess P(III) reagent has probably consumed the electrophilic fluorinating reagent. Switching the roles of halenium and halide was found to be detrimental. A complex mixture was obtained from the reaction with a chlorenium (*N*-chlorosuccinimide or *N*-chlorophthalimide) and a fluoride (n-Bu_4NF), and the desired product formation was negligible (entries 6 and 7). As proposed earlier, the introduction of a small fluorine substituent at the initial electrophilic addition step is beneficial for the subsequent nucleophilic displacement.

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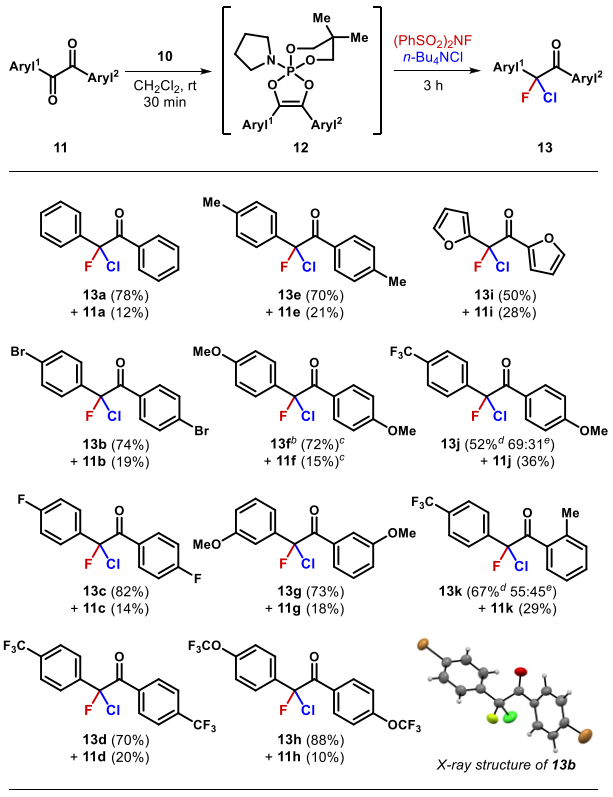
Moreover, the strong leaving group ability of chlorine may complicate the nucleophilic substitution step if chlorine is installed first. The favorable binding of fluoride to electron-deficient phosphorus may also be responsible for the lack of the desired reactivity, as well.

With the optimized conditions (Table 1, entry 1) in hand, a wide range of aryl−aryl 1,2-diketones (**11**) were surveyed (Scheme 1). (The preparation of **11** is described in the Supporting Information.) The reaction tolerated electron-withdrawing groups such as bromo, fluoro, and trifluoromethyl groups to give the corresponding geminal chlorofluorides (**13b−d**, respectively) in good yields. The slightly electron-rich *p*-tolyl derivative (**13e**) was also a suitable substrate. However, when the highly electron-donating methoxy group was introduced, the product **13f** became unstable. Even though fairly clean formation of **13f** was observed by ^{1}H NMR analysis of the crude mixture, the product was not isolable as it decomposed quickly on silica gel probably via the extrusion of the chlorine substituent. Nevertheless, the spectroscopic estimation of yield with an internal standard indicated that the reaction of the electron-rich substrate is equally efficient. A *meta* substituent (**13g**) could also be attached without any problem. In this case, methoxy groups were tolerated because the electron density is not donated to the geminal chlorofluorocarbon. To have a *para* oxygen substituent, the electron-donating ability must be substantially attenuated. Thus, by employing trifluoromethoxy groups, the product **13h** could be obtained in a high yield. An electron-rich heteroaromatic substrate, 2,2′-furil (**11i**), was also tolerated with only slightly diminished efficiency. Finally, unsymmetrical aryl−aryl 1,2-diketones were examined. From the reaction of an electronically biased substrate **11j**, the geminal chlorofluorides **13j** were isolated as an ∼7:3 mixture of constitutional isomers in 52% yield. Although a slight preference for the electron-poor site was observed, the selectivity was insignificant. Steric hindrance by an *ortho* substituent (**11k**) was not a sufficient controlling factor, either, resulting in essentially no site selectivity. 1,2-Diketones with two *ortho* substituents could not be prepared via the current synthetic route. The structure of geminal chlorofluoride was unambiguously established by single-crystal X-ray diffraction analysis of **13b**.[9]

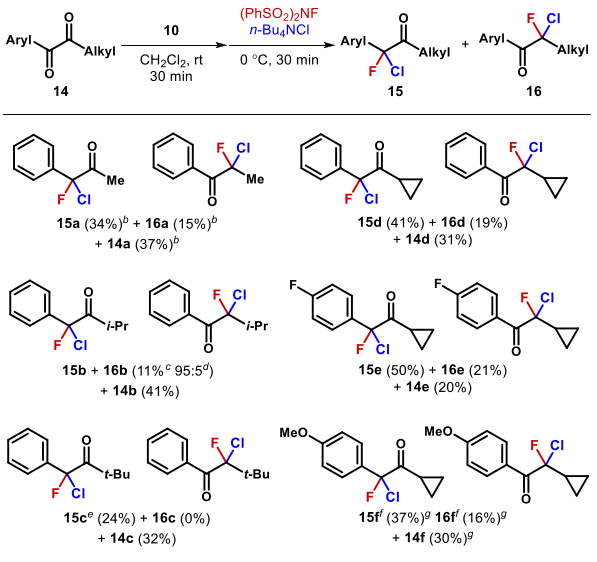
After slight modifications of reaction conditions, several aryl−alkyl 1,2-diketones (**14**) were examined (Scheme 2). (The preparation of **14** is described in the Supporting Information.) In this case, a mixture of constitutional isomers was generally obtained. The geminal chlorofluorination of phenyl methyl 1,2-diketone (**14a**) took place more preferentially at the benzylic carbon as it could be expected, providing **15a** and **16a** in 49% combined yield as an ∼2:1 isomeric mixture. In contrast to the aryl−aryl series, steric hindrance has a substantial influence on site selectivity. By employing a secondary alkyl substrate **14b**, the selectivity was greatly improved to 95:5. Furthermore, a single constitutional isomer **15c** was obtained from the reaction with a tertiary alkyl substrate **14c**. However, the rates were also significantly

Scheme 1. Tandem Geminal Chlorofluorination of Aryl−Aryl 1,2-Diketones[a]



[a]Reaction conditions: **11** (1.0 mmol), **10** (1.0 mmol), $(PhSO_2)_2NF$ (1.2 mmol), and *n*-Bu_4NCl (1.2 mmol) in CH_2Cl_2 (6.0 mL). Isolated yields after column chromatography are given. [b]Decomposed on silica gel. [c]Yield based on ^{1}H NMR analysis of the crude mixture with DMF as an internal standard. [d]Isolated yield of the mixture of constitutional isomers. [e]Isomeric ratio based on ^{1}H NMR analysis of the isolated mixture.

Scheme 2. Tandem Geminal Chlorofluorination of Aryl−Alkyl 1,2-Diketones[a]



[a]Reaction conditions: **14** (1.0 mmol), **10** (1.0 mmol), $(PhSO_2)_2NF$ (1.2 mmol), and *n*-Bu_4NCl (2.0 mmol) in CH_2Cl_2 (6.0 mL). [b]Isolated yield after column chromatography. [c]Isolated yield of a mixture of isomers. [d]Isomeric ratio based on ^{1}H NMR analysis of the isolated mixture. [e]Reaction at room temperature. [f]Decomposed on silica gel. [g]Yield based on ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.

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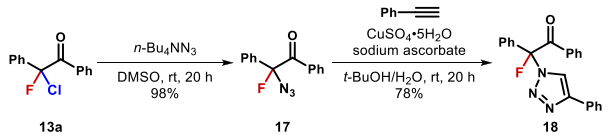
decreased at the same time, and unidentified side reactions that seemed to arise from α-halogenation and elimination also took place, resulting in low mass recovery. Interestingly, the cyclopropyl group turned out to be the most suitable alkyl group for this chemistry. The reaction of **14d** afforded the chlorofluoride products **15d** and **16d** in an increased 60% combined yield as an ~2:1 mixture of constitutional isomers. The slightly improved yield and selectivity were obtained from the reaction of an electron-poor substrate **14e**. In the case of electron-rich substrate **14f**, decomposition of the product during purification hampered the precise analysis, again. Thus, the yields were measured by ^{1}H NMR analysis of the crude mixture with an internal standard. Comparable yields were observed, and site selectivity was not affected by the electronic nature of the substrate.

As demonstrated previously by many research groups, geminal chlorofluorides are useful precursors to various organofluorides. Accordingly, a selective nucleophilic displacement of the chlorine substituent in our product **13a** was accomplished by the reaction with tetra-*n*-butylammonium azide (Scheme 3).[4c] The resulting geminal azidofluoride **17** could then be readily converted to the corresponding triazole **18** via Cu-catalyzed azide−alkyne cycloaddition.

Scheme 3. Derivatization of Geminal Chlorofluoride



A major concern for the combined use of electrophilic and nucleophilic halogens is the redox reaction between them, which may cause the halogen scrambling to give an inseparable mixture of geminal dihalides. Thus, the compatibility between F^+ and Cl^- was examined (eq 1). Unexpectedly, the slow

conversion of NFSI to phenylsulfonyl fluoride was observed in the presence of *n*-Bu_4NCl, and no sign of the oxidation of chloride was detected. This result explains the lack of halogen scrambling as well as the requirement of a slight excess of NFSI.

A reaction mechanism is proposed for the product formation and the starting material regeneration (Figure 3). Electrophilic fluorination of dioxaphospholene **12** generates an activated cationic intermediate **19**, which has two competing electrophilic sites. The subsequent nucleophilic displacement by

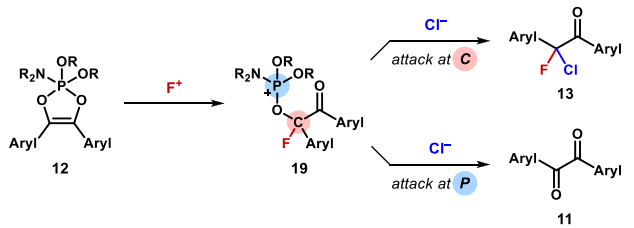
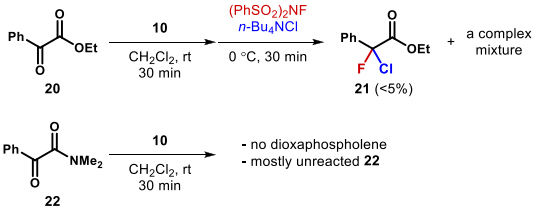


Figure 3. Proposed reaction mechanism.

chloride at the α-carbon affords the desired geminal chlorofluoride product **13**. On the other hand, the attack of a nucleophile at the phosphonium center results in the fragmentation to regenerate the 1,2-diketone starting material **11**. On the basis of this mechanistic proposal, modulation of steric and electronic property of phosphorus(III) reagents is currently being investigated to prevent the reactant regeneration and thus to improve the conversion.

In attempts to expand the substrate scope, a few other types of 1,2-dicarbonyl compounds were examined under the optimized conditions (Scheme 4). The dioxaphospholene

Scheme 4. Examination of Other 1,2-Dicarbonyl Compounds



formation between α-keto ester **20** and **10** did not proceed cleanly, and the subsequent treatment with halogenating reagents afforded only a small amount of the desired geminal chlorofluoride **21** in an impure form. α-Keto amide **22** remained mostly unreacted in the presence of **10**. Further investigation with α-keto carboxylic acid derivatives will be reported in due course.

In conclusion, we have developed an efficient synthetic method that gives access to a tetrasubstituted carbon with two different halogen substituents in a single step. The newly designed phosphoramidite allows the formation of non-dealkylatable dioxaphospholene as a suitable carbene surrogate for the combined use of electrophilic halenium and nucleophilic halide. This method can be applied to a variety of aryl−aryl as well as aryl−cyclopropyl 1,2-diketones, although the site selectivity is moderate for unsymmetrical substrates. The structure of geminal chlorofluoride was unambiguously established by single-crystal X-ray crystallography. In addition, the more reactive chlorine substituent could be selectively functionalized to give a tertiary alkyl fluoride. Further studies of site selectivity control and development of enantioselective variants are currently ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01258.

Experimental details, characterization data, and copies of NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1964847 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(9) CCDC 1964847 contains the supplementary crystallographic data for this study. 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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