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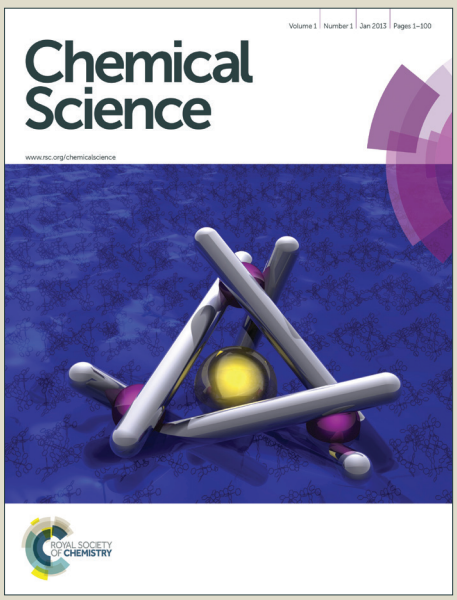





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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

# Regioselective Alkyl Transfer from Phosphonium Ylides to Functionalized Polyfluoroarenes†

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*Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX*

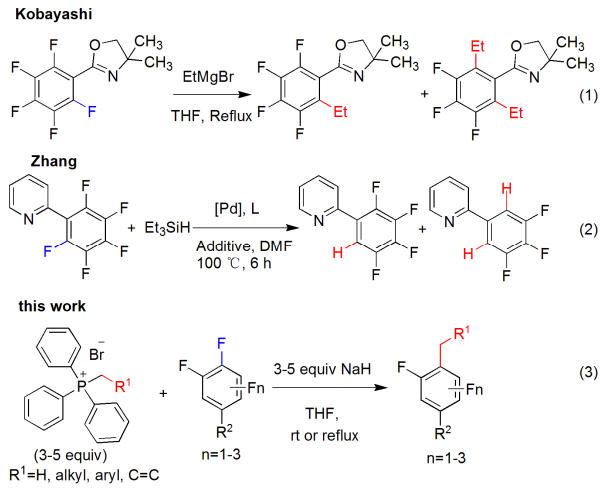
**DOI: 10.1039/b000000x**

**We report an unprecedented alkyl transfer from phosphonium ylide to polyfluoroarenes in a highly regioselective manner. This reaction allows the introduction of a variety of alkyl groups to the *para* position of functionalized polyfluoroarenes under mild conditions. The process is found to be compatible with several electrophilic functional groups such as carboxyl, ester, amide and cyano groups. NMR spectroscopy studies and deuterated labeling experiments reveal that the reaction proceeds via $S_NAr$ mechanism and the proton that is transferred to α-carbon of the alkyl group during the last C-P bond breaking step is from water.**

## Introduction

Carbon-carbon bond formation is undoubtedly one of the most important and fundamental transformations in organic chemistry. Fruitful achievements in this field during the past century have provided myriad methods for constructing various kinds of carbon-carbon bonds in organic compounds.[1] Nevertheless, the pursuit of new methodologies with high efficiency, superior selectivity, operational simplicity and broad functional group tolerance is still a continuing task for organic chemists.[2] Phosphonium ylides are mostly known for their use in Wittig reaction to convert ketones or aldehydes into alkenes.[3] Recently, a Michael addition-elimination type annulation reaction based on phosphonium ylide was also developed to construct bicyclic compounds.[4] Herein we report an unprecedented alkyl transfer from phosphonium ylides to polyfluoroarenes. The reactions proceeded smoothly under mild conditions without using any metal catalyst. The high regioselectivity of the alkyl transfer renders the strategy practically useful in synthesizing partially fluorinated compounds.

Fluorinated organic compounds have been widely used in the fields of pharmaceuticals, agrochemicals, biomedicine and materials science owing to their unique properties.[5] However, the syntheses of partially fluorinated compounds remain a great challenge in organic synthesis.[6] The main hurdles in the C-F activation or functionalization of polyfluoro-compounds are the poor chemo- and regio-selectivity as well as the limited compatibility with other functional groups.[7] Earlier work by Kobayashi and coworkers successfully demonstrated *ortho*-substitution of pentafluorobenzene with Grignard agent by using an intramolecular oxazolinyl group (Scheme 1, equation 1).[8] Recently, transitional metal-catalyzed regioselective C-F activation of polyfluoroarenes has been achieved by several groups through the introduction of proper ligands or directing groups.[9] For instance, Radius and coworkers reported selective C-F activation of polyfluoroarenes in Kumada and Suzuki-Miyaura-type cross-coupling catalyzed by an N-heterocyclic carbene stabilized nickel complex.[9c,10] Also, a palladium-catalyzed and chelation-assisted *ortho* selective C-F hydrodefluorination of perfluorobenzene derivatives was reported very recently (Scheme 1, equation 2).[11] However, many of those strategies still suffer from limited substrate scope and poor compatibility with other functional groups,[12] or in some cases the formation of inert intermediates with strong M-F bond.[13] During the investigation of the synthesis of a polyfluoroarene-substituted alkene, we discovered that phosphonium ylide could react with polyfluoroarenes regioselectively to afford alkylated polyfluoroaromatic compounds (Scheme 1, equation 3). The substrates can vary from functionalized trifluoro(hetero)arenes to pentafluoro(hetero)arenes, and the reaction occurs exclusively on the *para* position of the substituted polyfluoro(hetero)arenes. Another big advantage of the method is the broad tolerance of functional groups on polyfluoroarenes including electrophilic groups such as carboxyl, ester, amide and cyano groups, alkyl or aryl groups, and other halogen substitutions. The transfer of alkyl groups bearing aryl and allyl groups also occurred with moderate to good efficiency.

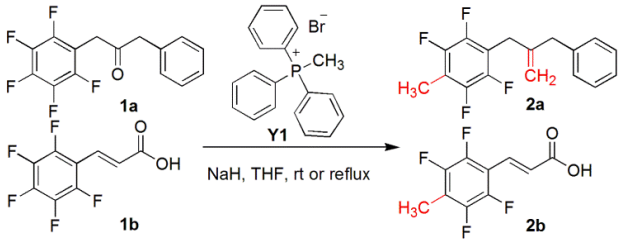



**Scheme 1** Selective C-F substitution or activation of polyfluoroarenes.

## Results and discussion

The regioselective methyl transfer process was occasionally found in a Wittig reaction when we attempted to synthesize a terminal alkene from **1a** (Table 1). n-Butyl lithium was first used as the base to extract the proton from the phosphonium salt **Y1** and the reaction resulted in a complex mixture (Table 1, entries 1 and 2). In contrast, when sodium hydride was used as the proton acceptor, *para*-methylated polyfluoroaromatic alkene **2a** was obtained in moderate yield at elevated temperature (Table 1, entry 6). Inspired by these initial results, we tested 3-pentafluorophenyl-acrylic acid **1b** as the substrate which contains an α,β-unsaturated carboxylic acid group. When **1b** reacted with **Y1** in the presence of 5 equivalents sodium hydride at refluxing temperature, nearly stoichiometric amount of *para*-methylated product **2b** was isolated (98%, entry 9). The presence of α,β-unsaturated carboxyl group in **1b** did not have any influence on the alkyl transfer efficiency. This prompted us to investigate the methyl transfer reaction of other functionalized polyfluoroarenes.

**Table 1** Condition screenings for methyl transfer to polyfluoroarenes.

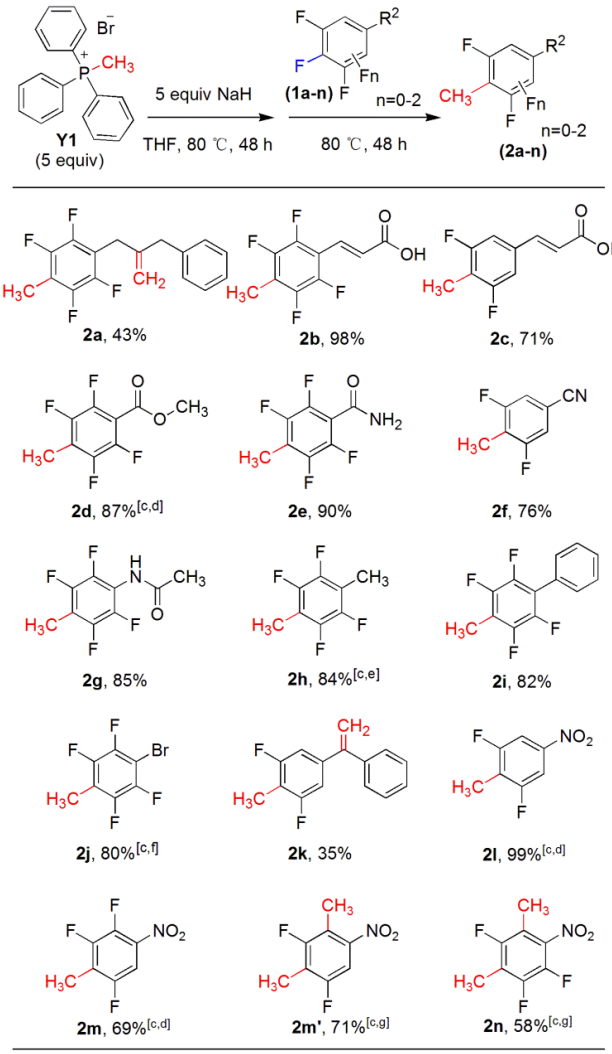



| entry | polyfluoroarene | phosphonium salt (equiv) | temp (℃) | alkali (equiv) | yield[a] |
|---|---|---|---|---|---|
| 1 | **1a** | 1.1 | rt | n-Butyl lithium (1.1) | complex mixture |
| 2 | **1a** | 2 | rt | n-Butyl lithium (2) | complex mixture |
| 3 | **1a** | 1 | 80 | NaH (1) | trace |
| 4 | **1a** | 1.2 | 80 | NaH (1.2) | trace |
| 5[b] | **1a** | 5 | rt | NaH (5) | < 5% |
| 6 | **1a** | 5 | 80 | NaH (5) | *43%* |
| 7[b] | **1b** | 5 | rt | NaH (5) | 17% |
| 8[b] | **1b** | 3 | 80 | NaH (3) | < 5% |
| 9 | **1b** | 5 | 80 | NaH (5) | *98%* |

[a] Isolated yields. [b] Determined by integration of the peaks in the $^{19}$F NMR spectra using α,α,α-trifluorotoluene as an internal standard.

A group of functionalized polyfluoroarenes were reacted with phosphonium salt **Y1** under the optimized conditions. To our delight, the regioselective methyl transfer process was found compatible with a broad range of functional groups (Table 2). Methylation of 3-(3,4,5-trifluoro-phenyl)acrylic acid **1c**, an analogue to compound **1b**, afforded **2c** in 71% yield which is lower than that of **1b** methylation. Furthermore, the reaction between 3-(3,4-difluorophenyl)acrylic acid and **Y1** did not give any desired product. These results implied that the multiple F-substitutions were prerequisite for the methyl transfer to occur smoothly. Next we turned our attention to other electrophilic

**Table 2** Methyl transfer to functionalized polyfluoroarenes.[a,b]



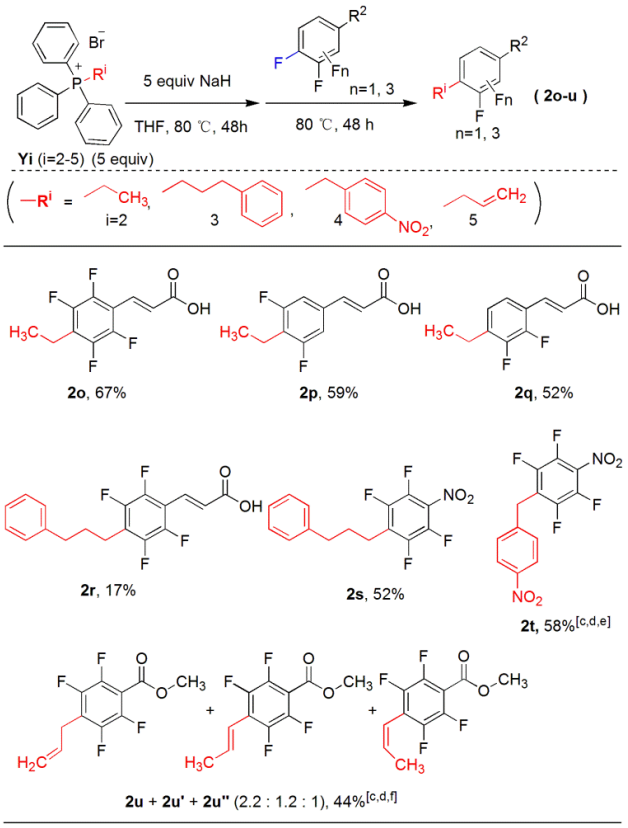

[a] Unless otherwise noted, the reactions were performed on a 1 mmol scale. [b] Isolated yields. [c] Determined by $^{19}$F NMR. [d] The reaction was carried out at the ambient temperature. [e,f] 5 and 10 mmol scale, respectively. [g] 10 equivalents of phosphonium salt and NaH were used. See the supplementary information for details.

functional groups, such as ester, amide and cyano groups, which are highly susceptible to nucleophiles. Interestingly, **2d**, **2e** and **2f** were obtained in 87%, 90% and 76% yield, respectively. This is in stark contrast to the conventional nucleophilic substitution by Grignard or alkyl lithium reagents where those electrophilic functional groups have to be protected.[14] To explore the scope of functional groups on polyfuoroarenes for the methyl transfer, we tested several other substrates. The reaction between 2,3,4,5,6-pentafluoroaniline and **Y1** resulted in a complex mixture. This might be because the amino group may compete with phosphonium ylide as the nucleophile and participate in the substitution reaction. We reasoned that protecting the amino group may inhibit this process and thus promote the efficiency of methyl transfer. Indeed, acetyl protected *N*-(2,3,4,5,6-pentafluorophenyl)acetamide **1g** reacted with **Y1** and gave the methylation product in 85% yield. We also checked the substrates with alkyl and aryl substitutions, and both afforded the desired products in good yields (**2h**, 84%; **2i** 82%). In addition, we chose

1-bromo-2,3,4,5,6-pentafluorobenzene **1j** as the substrate to see which position is more reactive under the attack of phosphonium salt **Y1**. The result showed that the fluorine on the *para* position was substituted by methyl group in high yield, which is consistent with literature reports.[6e] We also paid attention to a special type of substrates that contained both a polyfluoroaromatic moiety and a ketone or aldehyde group. Similar to compound **1a**, compound **1k** reacted with **Y1** to afford *para*-methylated polyfluoroaromatic alkene **2k** in 35% yield together with trace amount of methylated ketone.[15] However, when the ketone group was changed to an aldehyde group, the reaction resulted in a complex mixture. Finally, we focused on polyfluoronitrobenzenes which exhibited unusually high reactivity toward phosphonium ylides. When 3,4,5-trifluoronitrobenzene **1l** was reacted with phosphonium salt **Y1** in the methyl transfer reaction, we found that the reaction proceeded smoothly at ambient temperature in nearly quantitative yield (99%). Similarly, 2,3,4,5-tetrafluoronitrobenzene **1m** also reacted with **Y1** at ambient temperature to afford mono-methylated product **2m** albeit in lower yield (69%). Heating up the reaction of **1m** with **Y1** afforded the di-methylated product **2m′** in 71% yield, which has methyl substitutions on both 2- and 4-positions of the phenyl ring. When 2,3,4,5,6-pentafluoronitrobenzene **1n** was used in the reaction with **Y1**, the mixture of mono- and di-methylated products with varying ratios was obtained under different conditions. However, when the reaction was refluxed with **Y1** in large excess over **1n**, di-methylated product **2n** could be isolated as the sole product in 58% yield.

With the success of *para*-methylation of different functionalized polyfluoroarenes, we set out to investigate other alkyl transfer to polyfluoroarenes assisted by different phosphonium ylides (Table 3). Ethyl transfer with ethyltriphenylphosphonium bromide **Y2** to compounds **1b** and **1c** gave *para*-ethylated products in good yields (**2o**, 67%; **2p** 59%). Interestingly, 3-(2,3,4-trifluorophenyl)acrylic acid also reacted with **Y2** to afford an ethylated product **2q** in 52% yield. Characterization by $^{19}$F NMR, HMBC spectroscopy and X-ray crystallography revealed that the ethylation occurred on the *para*-position of the phenyl ring. This is an interesting finding because the *meta*-position might also be reactive owing to the F-substitutions on 2,4-positions; nevertheless, no *meta*-ethylated product was found in the product mixture. Following this trend, we turned to conduct the alkyl transfer reactions with more complex phosphonium salts. Alkyl transfer to compound **1b** was carried out in the presence of triphenyl-(3-phenylpropyl)phosphonium bromide **Y3** under the same conditions. It is notable that the phenylpropyl group was successfully transferred to the *para*-position of **1b** albeit in low yield (**2r**, 17%). It is possible that the bulky groups around the α-carbon of the alkyl chain in phosphonium ylides hindered the coupling process to some extend and thus resulted in low reaction yields. Strong electron-withdrawing groups such as nitro group on the phenyl ring (2,3,4,5,6-pentafluoronitrobenzene, **1n**) could promote the reaction yield to 52% (**2s**). Next, we tried other phosphonium salts that possess functional groups on the alkyl chain. (4-Nitrobenzyl)triphenylphosphonium bromide **Y4** and allyltriphenylphosphonium bromide **Y5** were reacted with **1n** and **1d** respectively, and both reactions produced the desired products

**Table 3** Scope expansion of phosphonium salts.[a,b]

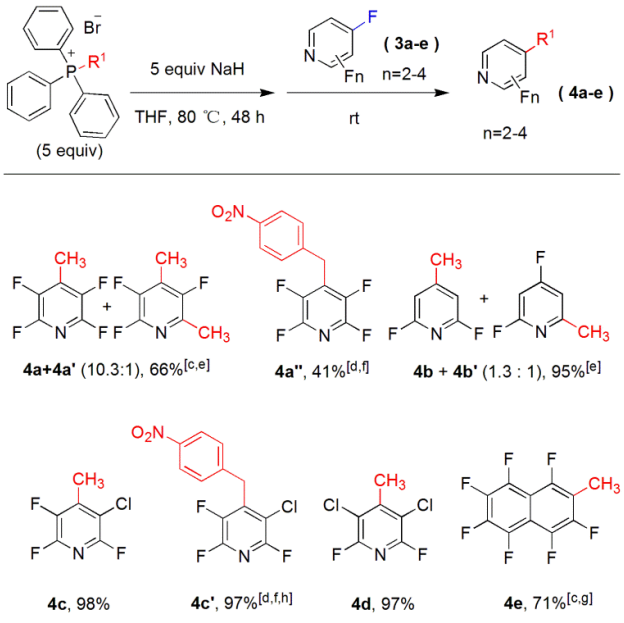



[a] Reactions were performed on a scale of 1-2 mmol. [b] Isolated yields. [c] Determined by $^{19}$F NMR. [d] Phosphonium salt and NaH were reacted at ambient temperature. [e] Reaction was performed in 1,4-dioxane at 110 °C. [f] Isomers of **2u**, **2u′** and **2u″** were isolated as a mixture and their proportion was determined by integration of the peaks in the $^{1}$H NMR spectra. See the supplementary information for details.

in low to moderate yields (**2t** 58%; **2u** + **2u′** + **2u″** 44%). The isomerization of the allyl group in **2u** resulted in the other two products **2u′** and **2u″** with double bond conjugated to polyfluoroarenes.

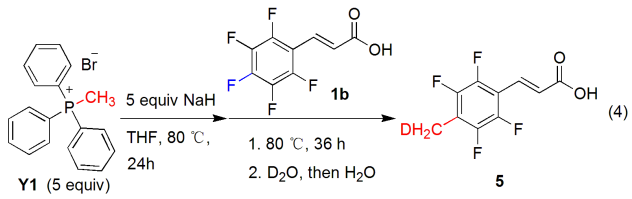
To expand the utility of the alkyl transfer method, we examined polyfluoroheteroarenes as the substrates. 2,3,4,5,6-Pentafluoropyridine **3a** was first tested in the reaction with 3 equivalents of phosphonium ylide **Y1** at 80 °C. It was found that the primary reactive position on polyfluoropyridine was also the *para*-position (**4a**, 60.2%). However, we identified another product (**4a′**, 5.8%) which was doubly methylated on both *para* and *ortho* positions. This result shows that the fluoro groups on heteroarenes are more reactive than their counterparts on polyfluoroarenes. The reaction of **3a** with (4-nitrobenzyl)triphenylphosphonium bromide **Y4** required a higher temperature of 110 °C and afforded the product **4a″** in 41% yield. In a similar case, 2,4,6-trifluoropyridine **3b** reacted with 5 equivalents of **Y1** to afford two methylated products **4b** and **4b′** in total 95% yield. Interestingly, both the products were mono-methylated with one methylation on para-position and the other methylation on *ortho*-position (1.3:1). It was surprising that when we used mono- or dichloro-substituted polyfluoropyridines as substrates, the alkyl transfer proceeded in exceptionally high yields (**4c** 98%, **4c′** 97%, **4d** 97%). We reasoned that might be because the chloro substitutions reduced the reactivity of

**Table 4** Alkyl tranfer to heterocyclic and fused ring polyfluoroarenes.[a,b]

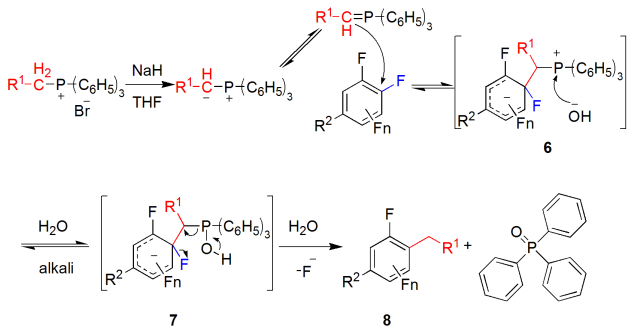



[a] Reactions were performed on a scale of 1-5 mmol. [b] Determined by $^{19}F$ NMR. [c] 3 equivalents of phosphonium salt and NaH were used. [d] Phosphonium salt and NaH were reacted at ambient temperature. [e,f,g] Reaction was performed at 80 °C, 110 °C and 60 °C, respectively. [h] Isolated yield.

polyfluoropyridines and simultaneously minimized their side reactions. To further exemplify the usefulness of the methodology, we also conducted the methyl transfer to octafluoronaphthalene **3e** which has a fused ring structure. The result showed that the mono-methylated compound **4e** could be isolated as the main product in 71% yield under optimized experimental conditions.



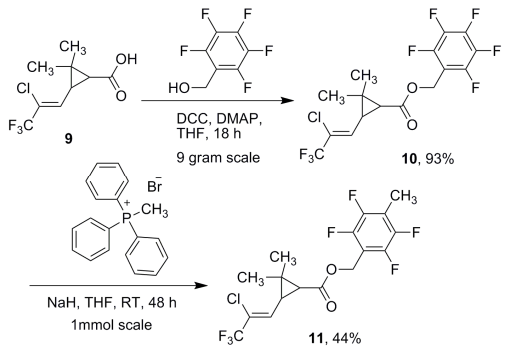

**Scheme 2** Deuteration experiment.




**Scheme 3** Proposed mechanism for the alkyl transfer from phosphonium ylide to polyfluoroarenes.

Although the alkyl transfer from phosphonium ylide to polyfluoroarenes is very likely a nucleophilic aromatic substitution, i.e. $S_NAr$ mechanism in this case, we performed mechanistic studies based on NMR spectroscopy to confirm the conclusion (see Supporting Information, Figure S1-3 and Scheme S1). In addition, it is not straightforward that which proton was added to the α-carbon of the alkyl chain when the phosphonium part was detached from the intermediate complex. We carried out a deuterium labeling experiment to confirm the source of this proton. The result showed that the proton transferred to α-carbon of the alkyl group during the last C-P bond breaking step was from water (Scheme 2). A detailed mechanism was illustrated in Scheme 3. Briefly, a carbanion center was initially formed by deprotonation of the phosphonium salt in the presence of strong base, followed by a regioselective nucleophilic attack on the polyfluoroarene to form a carbanion intermediate **6**.[16] Then, a rapid reversible attack on the P of the phosphonium center by hydroxide resulted in the formation of another intermediate **7**, which was subsequently hydrolyzed in the presence of alkali to afford **8** and triphenylphosphine oxide.[17] The extraordinary regioselectivity of this procedure might arise from the bulky steric hindrance around the phosphonium center which could guide the reactive site during the nucleophilic attack process (Scheme 3). The broad tolerance of functional groups on polyfluoroarenes in this process could be accounted for by a recent study that triphenylphosphonium ylides are approximately thousand times less reactive than the corresponding dimethylsulfonium ylides and about a million times less reactive than the analogously substituted pyridium ylides.[18]

With the alkyl transfer methodology in hand, we expected to employ the strategy in the practical synthesis of the compounds that contain polyfluoroarene moieties. Tefluthrin is a fluorine-containing pyrethroid and has been widely used as pesticide since the 1990s.[19] The key step of the reported synthesis of tefluthrin was the reaction between an acyl chloride and 2,3,5,6-tetrafluoro-4-methylbenzyl alcohol (Supplementary Information).[20] Although this step proceeded smoothly in 96.5% yield, it took a tediously long procedure to make the benzyl alcohol from commercially available materials.[21] It is obvious that the alkyl transfer reaction we developed can install the methyl group on the phenyl ring of tefluthrin at a later stage. Thus, we carried out the esterification reaction between the acid **9** and the readily available pentafluorobenzyl alcohol, followed by a methyl transfer step in the presence of phosphonium salt **Y1**. This two-step synthesis greatly shortened the synthetic route of tefluthrin and afforded the product in 41% overall yield which is comparable with the reported procedure.[20a] In addition, other derivatives of tefluthrin could be conveniently synthesized through this route.




**Scheme 4** Synthesis of tefluthrin.

## Conclusion

In summary, we have described an alkyl transfer from phosphonium ylide regioselectively to functionalized polyfluoroarenes under mild conditions. This work greatly expands the scope of defluorinative sp2-sp3 coupling mediated by nucleophiles. The high compatibility of the process with a broad range of functional groups makes it very useful for synthesizing polyfluoroarene derivatives. Those functional groups include electrophilic groups such as carboxyl, ester, amide and cyano groups, alkyl and aryl groups, and other halogens. When a molecule contains both polyfluoroarene and ketone groups, para-methylated aromatic alkenes were obtained as the main product. This method could also be applied to the alkylation of polyfluoroheteroarenes. Finally, we exemplified the utility of the method by synthesizing a fluorine-containing pesticide Tefluthrin via a new and much shortened synthetic route. This method is apparently useful for late-stage C-F modifications during the synthesis of polyfluoroarene-containing compounds. We expect to develop new C-F functionalization reactions by combining the alkyl transfer process and transition metal-catalyzed C-F activations.

## Acknowledgments

We are grateful to Prof. Jin-Quan Yu for his useful comments on the manuscript. This research was supported by the National Natural Science Foundation of China (No. 21175135), National Basic Research program of China (973 program, Nos. 2010CB933600 and 2013CB932800), and the "100 Talents" program of the Chinese Academy of Sciences.

## Notes and references

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† Electronic Supplementary Information (ESI) available: [Detailed experimental procedures, NMR and additional spectral data]. See DOI: 10.1039/b000000x/

1. a) R. A. Sheldon, I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, 2007; b) F. Diederich, P. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, 2008.
2. a) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nat Chem* 2009, **1**, 494-499; b) G. Li, R. Chen, L. Wu, Q. Fu, X. Zhang, Z. Tang, *Angew. Chem.* 2013, **125**, 8590-8594; *Angew. Chem. Int. Ed.* 2013, **52**, 8432-8436.
3. a) G. Wittig, U. Schöllkopf, *Chem. Ber.* 1954, **87**, 1318-1330; b) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* 1989, **89**, 863-927; c) P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev.* 2013, **42**, 6670-6696.
4. a) L.-W. Ye, X.-L. Sun, Q.-G. Wang, Y. Tang, *Angew. Chem.* 2007, **119**, 6055-6058; *Angew. Chem. Int. Ed.* 2007, **46**, 5951-5954; b) X.-L. Sun, Y. Tang, *Acc. Chem. Res.* 2008, **41**, 937-948.
5. a) D. R. Leser, *Am. J. Nurs.* 1982, **82**, 452-455; b) J. A. Wilkinson, *Chem. Rev.* 1992, **92**, 505-519; c) K. Müller, C. Faeh, F. Diederich, *Science* 2007, **317**, 1881-1886; d) H. P. Chiu, B. Kokona, R. Fairman, R. P. Cheng, *J. Am. Chem. Soc.* 2009, **131**, 13192-13193; e) Q. Zhou, A. Ruffoni, R. Gianatassio, Y. Fujiwara, E. Sella, D. Shabat, P. S. Baran, *Angew. Chem.* 2013, **125**, 4041-4044; *Angew. Chem. Int. Ed.* 2013, **52**, 3949-3952.
6. a) V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp, W. A. Herrmann, *Angew. Chem.* 2001, **113**, 3500-3503; *Angew. Chem. Int. Ed.* 2001, **40**, 3387-3389; b) N. Yoshikai, H. Mashima, E. Nakamura, *J. Am. Chem. Soc.* 2005, **127**, 17978-17979; c) N. Yoshikai, H. Matsuda, E. Nakamura, *J. Am. Chem. Soc.* 2009, **131**, 9590-9599; d) S. A. Johnson, C. W. Huff, F. Mustafa, M. Saliba, *J. Am. Chem. Soc.* 2008, **130**, 17278-17280; e) H. Amii, K. Uneyama, *Chem. Rev.* 2009, **109**, 2119-2183; f) H. L. Buckley, A. D. Sun, J. A. Love, *Organometallics* 2009, **28**, 6622-6624; g) M. F. Kühnel, D. Lentz, *Angew. Chem.* 2010, **122**, 2995-2998; *Angew. Chem. Int. Ed.* 2010, **49**, 2933-2936; h) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* 2011**,** **108**, 14411-14415; i) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* 2012, **492**, 95-99; j) D. Breyer, T. Braun, P. Klaring, *Organometallics* 2012, **31**, 1417-1424.
7. a) S. S. Laev, V. U. Evtefeev, V. D. Shteingarts, *J. Fluor. Chem.* 2001, **110**, 43-46; b) T. Saeki, Y. Takashima, K. Tamao, *Synlett* 2005, **2005**, 1771-1774.
8. Y. Inukai, K. Takuma, K. Toritani, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn* 1984, **57**, 225-231.
9. a) M. Aizenberg, D. Milstein, *Science* 1994, **265**, 359-361; b) T. Wang, B. J. Alfonso, J. A. Love, *Org. Lett.* 2007, **9**, 5629-5631; c) T. Schaub, P. Fischer, A. Steffen, T. Braun, U. Radius, A. Mix, *J. Am. Chem. Soc.* 2008, **130**, 9304-9317; d) M. E. Doster, S. A. Johnson, *Angew. Chem.* 2009, **121**, 2219-2221; *Angew. Chem. Int. Ed.* 2009, **48**, 2185-2187; e) A. D. Sun, J. A. Love, *Dalton Trans.* 2010, **39**, 10362-10374; f) A. D. Sun, J. A. Love, *J. Fluor. Chem.* 2010, **131**, 1237-1240; g) L. Keyes, A. D. Sun, J. A. Love, *Eur. J. Org. Chem.* 2011, **17**, 3985-3994; h) J. A. Panetier, S. A. Macgregor, M. K. Whittlesey, *Angew. Chem.* 2011, **123**, 2835-2838; *Angew. Chem. Int. Ed.* 2011, **50**, 2783-2786; i) X. F. Xu, H. J. Sun, Y. J. Shi, J. Jia, X. Y. Li, *Dalton Trans.* 2011, **40**, 7866-7872; j) Y. Nakamura, N. Yoshikai, L. Ilies, E. Nakamura, *Org. Lett.* 2012, **14**, 3316-3319; k) H. Lv, Y.-B. Cai, J.-L. Zhang, *Angew. Chem.* 2013, **125**, 3285-3289; *Angew. Chem. Int. Ed.* 2013, **52**, 3203-3207.
10. T. Schaub, M. Backes, U. Radius, *J. Am. Chem. Soc.* 2006, **128**, 15964-15965.
11. a) D. H. Yu, Q. L. Shen, L. Lu, *J. Org. Chem.* 2012, **77**, 1798-1804; b) D. Yu, L. Lu, Q. Shen, *Org. Lett.* 2013, **15**, 940-943; c) Z. Chen, C.-Y. He, Z. Yin, L. Chen, Y. He, X. Zhang, *Angew. Chem.* 2013, **125**, 5925-5929; *Angew. Chem. Int. Ed.* 2013, **52**, 5813-5817.
12. a) M. Ohashi, T. Kambara, T. Hatanaka, H. Saijo, R. Doi, S. Ogoshi, *J. Am. Chem. Soc.* 2011, **133**, 3256-3259; b) X. X. Yang, H. J. Sun, S. M. Zhang, X. Y. Li, *J. Organomet. Chem.* 2013, **723**, 36-42.
13. a) W. D. Jones, *Dalton Trans.* 2003, 3991-3995; b) J. Vela, J. M. Smith, Y. Yu, N. A. Ketterer, C. J. Flaschenriem, R. J. Lachicotte, P. L. Holland, *J. Am. Chem. Soc.* 2005, **127**, 7857-7870.
14. a) A. I. Meyers, B. E. Williams, *Tetrahedron Lett.* 1978, **19**, 223-226; b) D. J. Milner, *J. Organomet. Chem.* 1986, **302**, 147-152.
15. See the SI for structure and NMR information of the methylated ketone.
16. a) A. A. El-kateb, L. S. Boulos, L. T. Hennawy, H. A. Abdel-malek, *Phosphorus Sulfur Silicon Relat. Elem.* 1991, **60**, 275-279; b) J. Vicente, M. T. Chicote, J. Fernandez-Baeza, A. Fernandez-Baeza, P. G. Jones, *J. Am. Chem. Soc.* 1993, **115**, 794-796.
17. a) G. L. Keldsen, W. E. McEwen, *J. Am. Chem. Soc.* 1978, **100**, 7312-7317; b) N. S. Isaacs, O. H. Abed, *Tetrahedron Lett.* 1986, **27**, 1209-1210; c) S. M. Cairns, W. E. McEwen, *J. Org. Chem.* 1987, **52**, 4829-4831.
18. D. S. Allgaeuer, P. Mayer and H. Mayr, *J. Am. Chem. Soc.*, 2013, **135**, 15216-15224.
19. a) P. K. Michaelides, D. J. Wright, *Pestic. Sci.* 1997, **49**, 1-8; b) J. R. Prasifka, M. D. Lopez, R. L. Hellmich, P. L. Prasifka, *Pest Manag. Sci.* 2008, **64**, 30-36.

20. S. M. Brown, B. D. Gott, U.S. Patent 6,875,885, 2005.
21. a) D. C. Wang, Y. F. Jiang, U.S. Patent 7,312,366, 2007. b) See the SI for details.