Communication to the Editor

Rhodium-Catalyzed (Perfluoroalkyl)-olefination of Acetanilides Leading to Perfluoroalkylated Aromatics

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We have developed an efficient Rh-catalyzed (perfluoroalkyl)olefination reaction of acetanilides, which provides a versatile synthetic entry to a range of perfluoroalkylated compounds.

Key words perfluoroalkyl (R-F) group; olefination; C–H activation; acetanilide

Organic compounds containing fluoride are of particular interest in medicinal3–4 and materials sciences,5,6 as well as in catalyst design and numerous synthetic7–9 and catalytic10 studies have focused on introduction of a fluorine atom or trifluoromethyl group into organic molecules.12,13 Perfluoroalkylation has received less attention from the viewpoint of synthetic methodology,14,15 but perfluoroalkyl (R-F) groups have substantial utility as potent electron-withdrawing moieties, film-forming materials, fluorous tags and unique bulk properties, such as high melting point, low dielectric constant, low solubility in common organic solvents, high chemical stability, and surface hydrophobicity via self-assembly of R-F-chains according to the stratified dipole-array model.16 Therefore, we have been developing novel perfluoroalkylation methodologies, especially utilizing R-F-zinc reagents.20–22 Our previous work25 and work by other research groups28–32 has provided easy access to (hetero) aromatic compounds directly substituted with an R-F group (Chart 1).

On the other hand, it is sometimes necessary to tune or lessen the strongly electron-withdrawing effect of an R-F group on an aromatic ring and insertion of a one- or two-carbon spacer between the aromatic ring and R-F group would be an effective way to achieve this. Therefore, there is a need for a facile, efficient access to such compounds. Herein, we report a novel approach to synthesize perfluoroalkylated arenes with a C2-spacer.

Cross-coupling reaction between aryl Grignard reagents and 2-R-F-ethyl iodides catalyzed by Cu, developed by Fuchikami and colleagues,24 and Leitner and colleagues,35,36 as well as the Suzuki–Miyaura strategy developed by Ding and colleagues,37 can give the desired perfluoroalkylated arenes with a C2-spacer, albeit in moderate yields (Chart 2). Genêt and colleagues demonstrated an efficient synthesis of this class of compounds via palladium-catalyzed Heck reaction of arylidiazonium tetrafluoroborate with (perfluoroalkyl)ethylenes and subsequent hydrogenation.38 This Heck reaction is remarkably effective for β-(perfluoroalkyl)styrenes,39 although the diazonium salt is not an optimal electrophile due to its instability and potentially explosive nature (p-iodo- and p-bromotoluene are much less reactive in this system). Thus, a new and synthetically more benign method is still required. The most straightforward and atom-economic40,41 desirable route to β-(perfluoroalkyl)styrenes would be direct installation of a 2-R-F-ethenyl group onto aromatic rings by cleaving a C–H bond.

Herein, we report a (perfluoroalkyl)ethenylated reaction of arenes via Rh-catalyzed oxidative Heck reaction. The Heck-product has a perfluoroalkylated double bond, which can be manipulated to obtain various R-F-containing functionalities.44–46 As an initial trial, we used acetanilide (1a) and (perfluorohexyl)ethylene in the presence of a cationic Rh(II) catalyst under slightly modified Glorius olefination conditions.47–50 Gratifyingly, the desired olefinated product 2a was obtained, albeit in only 14% yield. Encouraged by this result, we set out to optimize the reaction conditions (Table 1). First of all, we examined the effect of the counter ion of the Rh-catalyst (Entries 1–4). By increasing the amount of the catalyst prepared from [RhCp*Cl2]2 and AgSbF6 to 1 mol%, the desired product 2a was obtained in 34% yield (Entry 1). 2a was formed in 52% yield by using AgOTf (Entry 2), and AgNTf2 gave 2a in even better yield (61%, Entry 3). Highly cationic Rh-catalyst bearing mononuclear-closo-dodecaborate, C8B11H10Br3,52 was not as effective as the OTf− and NTf2− counterparts (Entry 4 vs. Entries 2, 3). Omission of silver salt resulted in virtually no reaction and shows the necessity of a cationic character of the Rh-catalyst (Entry 5). Reaction at 100°C slightly improved the yield of 2a (64%, Entry 6).

Based on these results, screening of solvents was performed using AgNTf2 as the optimal activator of the Rh-catalyst. Good yields were obtained in poor yields in highly coordinating non-protic solvents such as N,N-dimethylformamide (DMF) (Entry 7). A chloronated solvent, 1,2-dichloroethane (DCE), afforded 2a in 20% yield accompanied by the β-fluoride elimination product (15%, Entry 8). Ether-based solvents were generally effective for this reaction (Entries 9, 10), and 1,2-dimethoxyethane (DME) was the best solvent, giving 2a in 67% yield (Entry 10). By elevating the reaction temperature to 120°C and increasing the amount of (perfluorohexyl)ethylene to 2.5 eq, 2a was obtained...
in 83% yield (Entry 11). Based on these results, the set of reaction conditions of Entry 11 was selected as optimal, and we examined the substrate scope under these reaction conditions (Table 2).

The substrate with a MeO group at the para-position 1b gave the desired product 2b in 80% yield. This reaction was easily scaled up to gram-scale and 2b was obtained in 62% yield (953 mg). Products containing halogens were obtained in slightly lower yields (2c–f). In the case of 4-iodoacetanilide (1f), the somewhat lower yield of this reaction is attributed to partial proto-deiodination, which was observed by GC/MS analysis. Introduction of a strongly electron-withdrawing CF\textsubscript{3} group significantly reduced the product formation (2g, 36% yield). Regioselectivity with meta-substituted anilides (1h–k) was very high and only the products olefinated at the 6-position were obtained (2h–k). With a CF\textsubscript{3}-group at the meta-position, the desired product 2h was obtained in 37% yield. Olefination of 3-chloroacetanilide (1i) proceeded in moderate yield (2i, 55% yield). An additional halogen atom on the aromatic ring resulted in poor conversion of the anilide 2j. On the contrary, electron-donating substituents such as a Me group promoted formation of the product, and 2k was obtained in 71% yield. These results clearly indicated that the electron density of the aryl ring plays an important role.

A Me group at the ortho-position to NHAc was well tolerated, and the product 2l was obtained in 60% yield. In addition, (nonafluorobutyl)ethylene was examined, and the C4-homoologue 2m was obtained in 72% yield.

Finally, we demonstrated elaboration of the double bond of the products 2a, 2b, and 2k (Chart 3). Hydrogenation proceeded cleanly in the presence of a catalytic amount of Pd/C under atmospheric pressure of H\textsubscript{2} gas to give R\textsubscript{F}-anilides with the saturated C\textsubscript{2} spacer, which are otherwise not trivial to synthesize.

In conclusion, we have developed a straightforward ac-
cess to 2-(perfluoroalkyl)ethenyl acetalanilides. This reaction proceeds in moderate to high yields with good chemoselectivity. The double bond adjacent to the R F-group was cleanly hydrogenated. Further studies on chemical elaborations of the double bond to provide diverse R F-compounds are underway.

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Conflict of Interest The authors declare no conflict of interest.

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References and Notes
1) Meanwell N. A., J. Med. Chem., 54, 2529–2591 (2011).
2) Müller K., Fuh C., Diederich F., Science, 317, 1881–1886 (2007).
3) Purser S., Moore P. R., Swallow S., Gouverneur V., Chem. Soc. Rev., 37, 320–330 (2008).
4) Isanbor C., O’Hagan D., J. Fluor. Chem., 127, 302–319 (2006).
5) Facchetti A., Mushrush M., Yoon M.-H., Hutchison G. R., Ratner M. A., Marks T. J., J. Am. Chem. Soc., 126, 13859–13874 (2004).
6) Le Y., Unemoto Y., Kaneda T., Aso Y., Org. Lett., 8, 5381–5384 (2006).
7) Ritter T., Day M. W., Grubbs R. H., J. Am. Chem. Soc., 128, 11768–11769 (2006).
8) Zimmer L. E., Mercer C., Gilmour R., J. Am. Chem. Soc., 125, 12672–12673 (2003).
9) For synthesis of CF3-containing (hetero)aromatics, see: Schlosser et al., Angew. Chem. Int. Ed., 54, 5342–5446 (2006).
10) Furuya T., Kamlet A. S., Ritter T., Nature (London), 473, 470–477 (2011).
11) For a comprehensive review on fluorination and fluoroalkylation reactions, see: Li L., Brennessel W. W., J. Fluor. Chem., 132, 1121–1128 (2001).
12) For reviews: Satoh T., Miura M., Eur. J. Org. Chem., 2002, 386–387 (2002).
13) For a seminal example of Ru-catalyzed C–H activation of acetanilides, see: Stuart D. R., Bertrand-Laperle M., Burgess K. M. N., J. Am. Chem. Soc., 130, 1645–1653 (2008).
14) For a review on fluorosolid-phase extraction, see: Barata-Vallejo S., Bonesi S. M., Postigo A., Acc. Chem. Res., 5, 6298–62518 (2015).
15) For a comprehensive review, see: Barata-Vallejo S., Bonesi S. M., Postigo A., RSC Adv., 5, 320–359 (2015).
16) For synthesis of CF3-containing (hetero)aromatics, see: Schlosser et al., Angew. Chem. Int. Ed., 54, 5342–5446 (2006).
17) For a review on perfluoroalkyl organometallics in organic synthesis, see: Petrov V. A., J. Org. Chem., 60, 3423–3426 (1995).
18) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Science, 354, 1471–1477 (1991).
19) For a review: Patureau F. W., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
20) For more details, see Supplementary Materials.
21) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
22) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
23) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
24) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
25) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
26) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
27) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
28) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
29) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
30) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
31) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
32) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
33) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
34) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
35) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
36) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
37) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
38) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
39) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
40) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
41) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).
42) For a review: Patureau F. W., Wencel-Delord J., Glorius F., Angew. Chem. Int. Ed. Engl., 34, 259–291 (1995).