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(XantPhos)AgBr as a cheap and readily available catalyst for the bromofluorocyclopropanation of electron-rich alkenes

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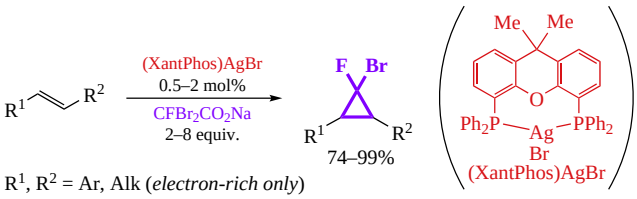
A silver phosphine complex (XantPhos)AgBr proved to be a cheap and readily accessible catalyst for bromofluorocyclopropanation of electron-rich alkenes with $CFBr_2CO_2Na$. Ozonolysis followed by treatment with $NaHSO_3$ was shown to be an effective protocol to purify *gem*-bromofluorocyclopropanes from unreacted alkene precursors.



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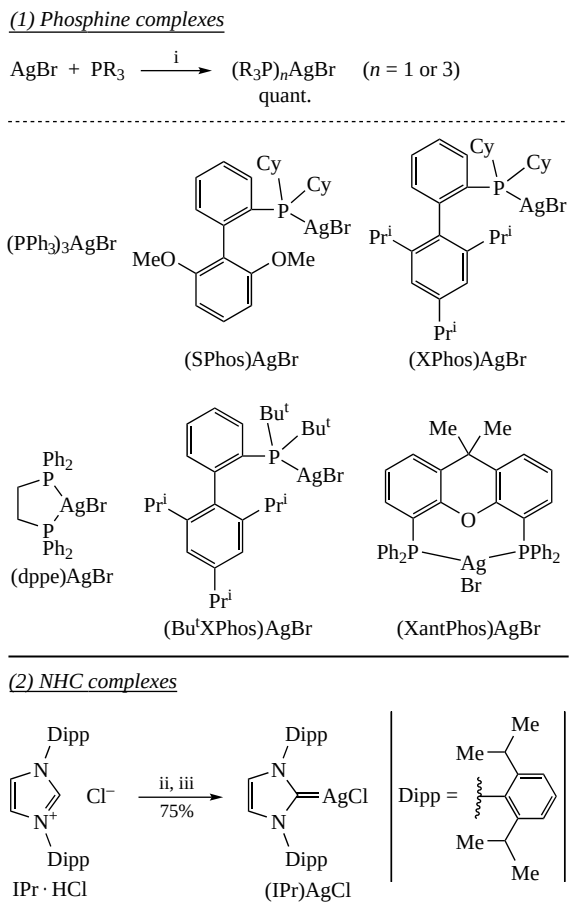
Organofluorine compounds represent a widely growing area of synthetic and medicinal chemistry due to extraordinary effect of fluorine on biological activities.[1–3] Fluorinated cyclopropanes are currently among the most extensively studied compounds.[4,5] Since discovery in 2015,[6] transition metal-catalyzed ring-opening of *gem*-difluorocyclopropanes leading to nucleophile-modified fluoroalkenes have gained recognition.[7–24] However, the serious disadvantage of these processes is the restriction to a chemotype of monoaryl-substituted *gem*-difluorocyclopropanes. On the other hand, relative *gem*-bromofluorocyclopropanes undergo Cu-catalyzed ring-opening much easier; even di-, tri- or even tetrasubstituted cyclopropanes[25,26] can react thus providing facile regio- and stereoselective synthesis of various functionalized fluoroalkenes (see Online Supplementary Materials, Scheme S1).[27–29] *gem*-Bromofluorocyclopropanes can also serve as good precursors for monofluorocyclopropanes,[30–34] which is a valuable alternative to known direct monofluorocyclopropanation methods.[35,36]

Recently we have developed an efficient bromofluorocyclopropanation procedure applying (NHC)AgCl as a catalyst for decarboxylation of $CFBr_2CO_2Na$.[37] Although syntheses of NHC-complexes seem to be simple, they do not always proceed cleanly and reproducibly. In certain cases consumption of initial NHC·HX salt was not complete, or the resulting (HNC)AgX complexes were contaminated with ionic complexes $(NHC)_2Ag^+X^-$ or $(NHC)_2Ag^+AgX_2^-$ (X = halogen),[38–42] thus requiring chromatographic purification. On the contrary, silver phosphine complexes are much more synthetically accessible whereas many phosphines are cheap and commercially available. Therefore, herein we have shown the applicability of silver phosphine complexes as catalysts for bromofluorocyclopropanation of electron-rich alkenes.

The required silver phosphine complexes were prepared by mixing the appropriate ligand with AgBr in CH_2Cl_2 followed by evaporation of the resulting solution, which afforded almost pure complexes in quantitative yields (Scheme 1). In contrast, synthesis of NHC complex (IPr)AgCl was more time-consuming and required prolonged heating of IPr·HCl, precursor of carbene ligand, with freshly precipitated Ag_2O in water or CH_2Cl_2. However, in our hands, these reactions proceeded with variable success, and in a half of cases chromatographic purification from side $(IPr)_2Ag^+X^-$ (X^- = Cl^- or $AgCl_2^-$) was required (see Scheme 1).



Scheme 1 *Reagents and conditions*: i, AgBr (1 equiv.), PR_3 (1–3 equiv.), CH_2Cl_2, room temperature, 30 min; ii, IPr·HCl (1 equiv.), Ag_2O (0.65 equiv.), H_2O, 100 °C, 48 h; iii, column chromatography.

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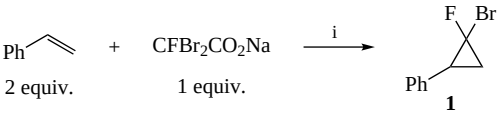


Scheme 2 *Reagents and conditions*: i, (L)AgBr, $ClCH_2CH_2Cl$, 80 °C (see Table 1).

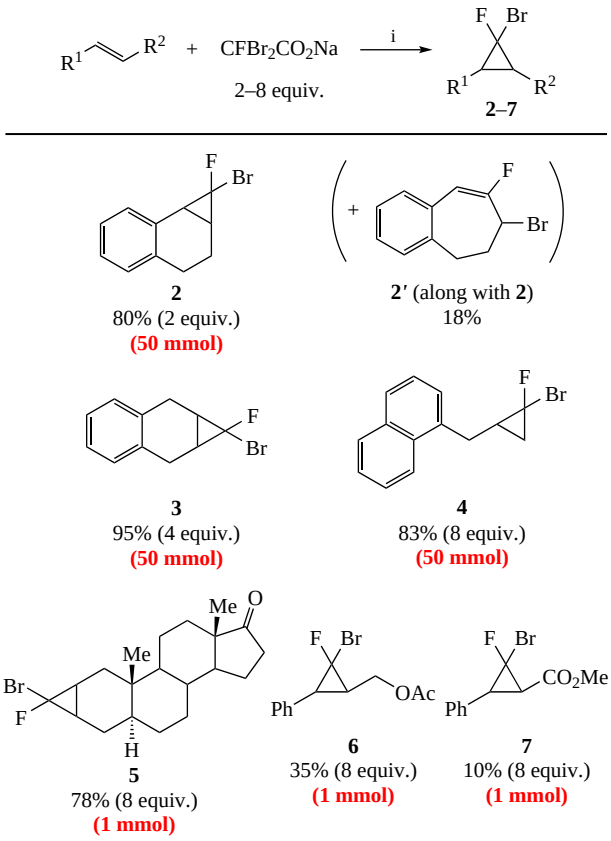
Table 1 Ligand screening for the bromofluorocyclopropanation of styrene.[a]

Entry	Ligand	Yield (%)[d]	Price ($)[e]
1	IPr[b]	75	49.6
2	PPh_3[c]	trace	0.04
3	dppe	5	0.9
4	SPhos	20	1.3
5	XPhos	45	1.5
6	Bu^{t}XPhos	55	2.1
7	XantPhos	80	1.6

[a] *Reaction conditions*: styrene (1.0 mmol), (XantPhos)AgBr (2 mol%), $CFBr_2CO_2Na$ (2–8 equiv.), $ClCH_2CH_2Cl$, 80 °C, 5–72 h. [b] As (IPr)AgCl. [c] As $(PPh_3)_3AgBr$. [d] Yields based on $CFBr_2CO_2Na$ as the limiting reagent were determined by calibrated GC and given to the nearest 5%. [e] Approximate prices (per 1 mmol) of (L)AgX complexes were calculated based on https://www.macklin.cn/en/catalogue.

Initially, we studied different phosphine complexes of AgBr in the cyclopropanation of styrene. To better compare the selectivity of $CFBr_2CO_2Na$ decomposition to the target bromofluorocarbene and its interception by alkene, we used a two-fold excess of styrene in the model reactions (Scheme 2, Table 1). The carbene ligand IPr used in the previous work gave 75% yield of cyclopropane **1** (entry 1). Among the phosphine ligands, PPh_3 and dppe were inefficient and provided only trace amounts of **1** (entries 2, 3). Buchwald phosphine ligands SPhos, XPhos and Bu^{t}XPhos were more efficient and gave **1** in moderate yields (entries 4–6). The best result was obtained with XantPhos, where the yield was even slightly higher than that with IPr (entries 7 *vs.* 1). A comparison of the costs of phosphine complexes with those of carbene complexes shows a significant advantage of the phosphine ones (see Table 1).

Thus, with (XantPhos)AgBr as the catalyst of choice, we further investigated its synthetic potential on a series of model alkenes, including multi-gram loadings (Scheme 3).† Thus, 1,2-dihydronaphthalene proved to be an active interceptor of :CFBr, allowing the preparation of the corresponding cyclopropane **2** in almost quantitative yield. However, compound **2** undergwent facile electrocyclic ring-opening under the elevated temperature of the reaction.[43] As the result, a mixture of **2** and 2-fluoroallylic bromide **2′** was formed in a ratio of 82 : 18, which, nevertheless, is not an obstacle to its further synthetic use.[26,44,45]



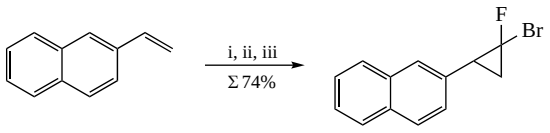
Scheme 3 *Reagents and conditions*: alkene, (XantPhos)AgBr (2 mol%), $CFBr_2CO_2Na$ (2–8 equiv.), $ClCH_2CH_2Cl$, 80 °C, 5–72 h. Yields for **6** and **7** were derived from ^{19}F NMR.

Less active 1,4-dihydronaphthalene and α-allylnaphthalene required longer heating and the use of greater excess of $CFBr_2CO_2Na$ up to 4 and 8 equiv., however, this allowed us to obtain high yields of cyclopropanes **3** and **4**, respectively (see Scheme 3). We have also successfully cyclopropanated 5α-androst-2-en-17-one to access the corresponding fluoro steroid **5** in good yield. However, alkenes with electron-withdrawing substituents are much more difficult to cyclopropanate. For example, cinnamyl acetate was converted into cyclopropane **6** in a moderate yield only after prolonged heating while methyl cinnamate gave only 10% of the target cyclopropane **7** (see Scheme 3).

It should be noted that an excess of $CFBr_2CO_2Na$ is to be adjusted for each new alkene, and this may not always be justified in terms of $CFBr_2CO_2Na$ consumption and/or time cost. However, the separation of alkenes and corresponding dihalocyclopropanes is not a straightforward task. For large quantities and relatively low-boiling substances, fractional distillation works well. Meanwhile, for scales lower than 10–20 g or for heavy compounds, distillation is impeded. Column chromatography is generally not good for the separation of alkenes and dihalocyclopropanes of close polarity.

We have noted that ozonolysis might be an easy and effective method to convert residual alkene into the carbonyl compound that will be easier to separate off. Cyclopropanation of 2-vinylnaphthalene **8** with 0.5 mol% (XantPhos)AgBr loading provided only *ca.* 80% conversion after 1 day of heating (Scheme 4). Instead of further heating with more $CFBr_2CO_2Na$,

† *General procedure*. A mixture of $CFBr_2CO_2Na$ (2 equiv.) and (XantPhos)AgBr (2 mol%) was dried under vacuum (0.1–0.2 Torr) for 1 h with stirring of these solids by magnetic stirrer. Next, under argon a solution of alkene (1.0 equiv., 1–50 mmol) in 1,2-dichloroethane (1 ml per 1 mmol of alkene) was added, and the reaction vessel was placed on an oil bath preheated to 80 °C while keeping it open to an argon line. After heating for 5 h, an aliquot was taken, it was diluted with hexane and analyzed by GC. If the reaction was not complete, additional $CFBr_2CO_2Na$ (2 equiv.) freshly dried under vacuum was added, and heating was continued for 21 h more (GC monitoring was continued and more $CFBr_2CO_2Na$ was added until complete conversion of alkene). After the reaction was complete, the mixture was evaporated with neutral Celite, and the crude product was washed out with hexane/Et_2O mixture (10 : 1). At this stage, the product may be pure enough according to NMR (as for **2**–**4**), or required chromatographic purification (as for **5**). In the cases of cyclopropanes **6** and **7**, after 8 equiv. of $CFBr_2CO_2Na$ were consumed and the reaction was heated for a total of 72 h, a lot of initial alkenes remained. Therefore, the reactions were stopped, subjected to work-up, and the residue was analyzed by ^1H and ^{19}F NMR. The yields were determined by ^{19}F NMR with 4-fluorobenzotrifluoride as an internal standard. ^1H and ^{19}F NMR data of **6** and **7** are in a full agreement with previous report.[37]



8 **9**

Scheme 4 *Reagents and conditions*: i, alkene **8**, (XantPhos)AgBr (0.5 mol%), $CFBr_2CO_2Na$ (2 equiv.), $ClCH_2CH_2Cl$, 80 °C, 24 h (~80% conversion); ii, O_3, CH_2Cl_2, –78 °C, then Me_2S, room temperature; iii, $NaHSO_3$ (saturated), MeOH, H_2O.

the crude product was isolated and subjected to ozonolysis during which product **9** remained intact while unreacted olefin **8** was converted into 2-naphthaldehyde (see Online Supplementary Materials, Scheme S2). The aldehyde was readily removed by washing with $NaHSO_3$ giving the corresponding hydroxy sulfonate,[46] and pure cyclopropane **9** was isolated after simple filtration through silica.

In summary, we have proposed a silver phosphine complex, (XantPhos)AgBr, as a cheap and readily accessible catalyst for bromofluorocyclopropanation of olefins with $CFBr_2CO_2Na$. This catalyst readily worked in the cases of electron-rich alkenes. Additionally, we have shown that ozonolysis is an effective and easy means to purify *gem*-bromofluorocyclopropanes from unreacted alkene precursors.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.023.

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