Homogeneous Catalysis

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Copper-Catalyzed Hydrodefluorination of Fluoroarenes by Copper Hydride Intermediates**

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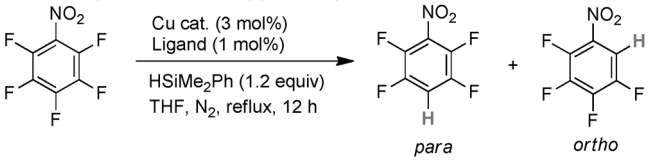
C–F bond activation attracts much attention because of the rapid growth of fluorocarbons in pharmaceuticals, agrochemicals, and new materials.[1] Such transformations not only provide new routes to the fluorinated organics, but also offer a fundamental understanding for C–F bond cleavage and functionalization.[2] Previous experimental and theoretical studies demonstrated the effectiveness of late transition metals (group 8–10) such as Fe, Ru, Os, Co, Rh, Ir, Ni, Pd, and Pt for their electron-rich nature and the relatively weak M–F bonds,[2c,3] which are important for catalytic functionality. Recently, we explored the reactivity of group 11 metal complexes and found that gold(I) complexes have good catalytic reactivity toward hydrodefluorination (HDF) of fluoroarenes.[4] Despite the tremendous progress made, most catalytic systems suffered from either low catalyst turnovers, limited substrate scope, or harsh reaction conditions. For example, gold(I) complexes are reactive only for the substrates with strong electron-withdrawing substituents, and their efficiency was greatly dependent on the electronic-donating additives.[5] To address these issues, we continued to explore the more-active group 11 metals such as copper, as we were inspired by the success of gold. In this context, we report herein the first example of a copper(I)-catalyzed HDF of fluoroarenes, and it features high reactivity, good regioselectivity, and a broad substrate scope.

Since Subramanian and Manzer reported the CuF_2-mediated fluorination of aromatics,[6] copper-catalyzed C–F bond formation has been developed by the groups of Hartwig, Lectka, and others.[7] In contrast, for catalytic C–F bond activation, copper has been rarely studied. Ribas and coworkers recently showed that a Cu^I/Cu^{III} redox cycle activated C–X bonds (X = halogens) using triazamacrocyclic ligand, thus indicating an oxidative addition mechanism.[7a] Herein, we found that for HDF reactions, copper hydrides exhibited an unprecedented reactivity toward C–F bonds. Moreover, density functional theory (DFT) calculations suggest that C–F bond activation by copper hydrides proceeds through a mechanism involving nucleophilic attack, and represents an alternative strategy for copper activating C–F bonds.

At the outset of our study, we searched for optimal HDF reaction conditions for perfluoronitrobenzene (PFNB). We first applied the our previous catalytic gold system but replaced gold(I) with $[Cu(MeCN)_4PF_6]$. Screening silanes (see Table S1 in the Supporting Information) such as $HSi(OMe)_3$, $HSiEt_3$, PMHS, H_2SiPh_2, and $HSiMe_2Ph$, showed that $HSiMe_2Ph$ was the best hydrogen source (conv. 40%). Solvent screening resulted THF providing the highest yield (60%; see Table S2 in the Supporting Information). We then examined ligand effects and the results are listed in Table 1. In the absence of a ligand and in the presence of monodentate phosphine such as PPh_3, PCy_3, and $[P(tBu)_2(o\text{-biphenyl})]$, no HDF product was observed (entries 1–4). For bidentate phosphine ligands, 1,2-bis(diphenylphosphino)benzene (BDP) led to a higher yield (90%; entry 9) compared to those obtained with ligands such as dppe, binap, Xantphos, and *t*BuXantphos (entries 5–8). The regioselectivity for *para*/

Table 1: Optimization of copper-catalyzed HDF of PFNB.[a]



Entry	Catalyst	Ligand[b]	Conv. [%][c]	Yield (*para*/*ortho*)[c]
1	$Cu(MeCN)_4PF_6$	–	0	0
2	$Cu(MeCN)_4PF_6$	PPh_3	0	0
3	$Cu(MeCN)_4PF_6$	PCy_3	0	0
4	$Cu(MeCN)_4PF_6$	$P(tBu)_2$(*o*-biphenyl)	0	0
5	$Cu(MeCN)_4PF_6$	dppe	12	90 (57:43)
6	$Cu(MeCN)_4PF_6$	binap	42	100 (58:42)
7	$Cu(MeCN)_4PF_6$	*t*BuXantphos	0	0
8	$Cu(MeCN)_4PF_6$	Xantphos	60	100 (61:39)
9	$Cu(MeCN)_4PF_6$	BDP	90	100 (48:52)
10	CuCl	BDP	0	0
11	$Cu(OAc)_2\cdot H_2O$	BDP	35	100 (55:45)
12	$CuCl_2\cdot 2H_2O$	BDP	0	0
13	CuCl/KO*t*Bu	BDP	98	100 (60:40)
14	CuCl/KO*t*Bu[d]	BDP	92	100 (58:42)

[a] Reaction conditions: 0.015 mmol copper salt, 0.005 mmol ligand, 0.5 mmol PFNB, and 0.6 mmol $HSiMe_2Ph$ were refluxed in 2 mL THF for 12 h. [b] Structures of ligands are shown in Scheme S1 of the Supporting Information. [c] Conversion and yield were determined by integration of the peaks in the ^{19}F NMR spectra using $CFCl_3$ as an internal standard. [d] Reaction conditions: 0.015 mmol copper salt, 0.005 mmol ligand, 5.0 mmol PFNB, and 6.0 mmol $HSiM_2Ph$ were refluxed in THF for 48 h.

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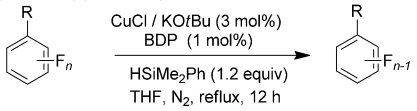
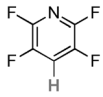
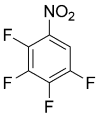
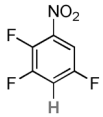
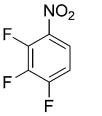
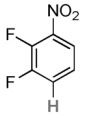
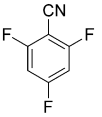
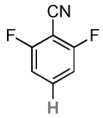
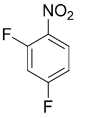
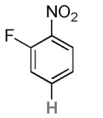
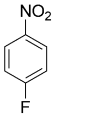
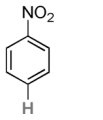
Table 2: Scope of copper-catalyzed HDF of fluoroarenes.[a]



Entry		Substrate	Product	Conv. [%][b]	Yield [%][b]
					
1	**1**	R = NO_2	R = NO_2	98	100 *p/o* = 60:40
2	**2**	R = CN	R = CN	95	100 *p/o* = 96:4
3	**3**	R = CF_3	R = CF_3	95	100
4[c]	**4**	R = F	R = F	70	100
5[c]	**5**	R = Cl	R = Cl	50	100
6[c]	**6**	R = Br	R = Br	50	100
7[c]	**7**	R = H	R = H	60	100
8[c]	**8**	R = OMe	R = OMe	20	100
9	**9**	R = COMe	R = COMe	80	40[d]
10	**10**	R = CHO	R = CH_2OH	78	0[e]
11	**11**	R = COOEt	R = COOEt	76	100
12	**12**	R = –≡–TMS	R = –≡–TMS	70	100
13	**13**			95	100
14	**14**			95	100 *p/o* = 78:22
15	**15**			85	95[f] *p/o* = 92:8
16[c]	**16**			88	100
17	**17**			84	76[g] *p/o* = 55:45
18	**18**			70	35[h]

[a] Reaction conditions: CuCl/KO*t*Bu 0.015 mmol, BDP 0.005 mmol, substrate 0.5 mmol, and $HSiMe_2Ph$ 0.6 mmol were refluxed in THF for 12 h. [b] Conversion and yield were determined by integration of the peaks in ^{19}F NMR spectroscopy using $CFCl_3$ as an internal standard. The *p/o* ratios show the regioselectivity for the *para* to *ortho* positions. [c] BDP ligand (5 mol%). [d] Side product was 1-(perfluorophenyl)ethanol. [e] The product was pentafluorophenylmethanol. [f] Side product was 2,3,4-trifluoroaniline. [g] Side product was 2,4-difluoroaniline. [h] Side product was 4-fluoroaniline.

ortho substitution was approximately 6:4, which is independent of the ligand type.

Copper salts were also examined, wherein CuCl and $CuCl_2$ showed no reactivity (Table 1, entries 10 and 12), and $Cu(OAc)_2$ exhibited moderate reactivity with a product yield of 35% (entry 11). CuCl/KO*t*Bu afforded the HDF product in high yield (98%, entry 13). Even when using 0.1 mol% BDP, 90% conversion of PFNB was obtained within 48 hours (entry 14), and is comparable to that obtained using a gold catalyst.[4] The ratios for *para* to *ortho* substitution were approximately 6:4, independent of copper salts.

With the optimal reaction conditions in hand, we surveyed the scope of substrates and the results are shown in Table 2. For pentafluoroarenes having electron-withdrawing substituents such as NO_2, CN, and CF_3 (**1**–**3**), higher reactivity (entries 1–3) was observed than for **4**–**12** (entries 4–12). With the electron-donating OMe as a substituent, the conversion fell to 20% (entry 8), thus indicating the electronic effect of the substrates on the efficiency of the HDF reaction. Examination of the functional-group tolerance indicated that the nitro, ester, and alkynyl substituents remained intact (entries 1, 11, and 12), whereas acetyl and formyl substituents were partially (entry 9) or completely (entry 10) reduced. For pentafluoropyridine, both a high yield (95%) and regioselectivity for the *para* position (entry 13) were achieved. Less-fluorinated substrates such as tetrafluoro- and trifluoroarenes (**14**–**16**) exhibited good reactivity (entries 14–16). To our delight, some kinetically inert fluoroarenes such as **17** and **18** could be hydrodefluorinated (entries 17 and 18) without using strong bases,[10] albeit with moderate chemoselectivity (76 and 35%, respectively). Compared with the previous catalytic systems with Rh,[8] Fe,[9] Ru,[10] and Au,[4,5] the catalytic copper system has several features: 1) high reactivity, for example, the TOF for C_6F_6 is up to 1.1 h^{-1}; 2) broad substrate scope; and 3) high regioselectivity as most substrates prefer to undergo HDF at the *para* position.

In catalytic systems containing Cu^I and a silane, copper hydrides are believed to be the active intermediates, and have been extensively studied in the catalytic reduction of C=C, C=O, C=N, and even C≡C bonds.[11] Besides that, metal hydrides played important roles in C–F bond activation, especially HDF.[8–10,12] Thus, we envisaged that copper hydrides generated in situ in our catalytic system might be active intermediates. Indeed, the reaction between $HSiMe_2Ph$ and $Cu(MeCN)_4PF_6$, in the presence of BDP afforded copper hydride (see Figure S1 in the Supporting Information).[11h] Addition of PFNB resulted in the HDF product. However, a large excess of $HSiMe_2Ph$ is necessary to observe the copper hydride formation, thus making it difficult to observe the reactivity of copper hydride toward C–F bonds directly.

To circumvent this problem, we adapted the method, reported by Lipshutz and Frieman, for preparation of a copper hydride.[11e] Treatment of $[\{(Ph_3P)CuH\}_6]$ (1/6 equiv) with BDP (1 equiv) in C_6D_6 led to the disappearance of the $[\{(Ph_3P)CuH\}_6]$ signal at $\delta = 3.51$ ppm, together with the appearance of a new peak at $\delta = 0.51$ ppm (Figure 1 A). By using $[\{(Ph_3P)CuD\}_6]$ to replace $[\{(Ph_3P)CuH\}_6]$, a peak appeared at $\delta = 0.53$ ppm in the ^2H NMR spectrum (Figure 1 B), thus confirming this new hydride transferring from $[\{(Ph_3P)CuD\}_6]$. Compared to the chemical shift of the copper hydride generated by $HSiMe_2Ph$ ($\delta = 1.42$ ppm), the upfield shifted hydride signal might be due to PPh_3 coordination.[13] $^1H\{^{31}P\}$ NMR analysis at 213 K in $[D_8]$THF confirmed the

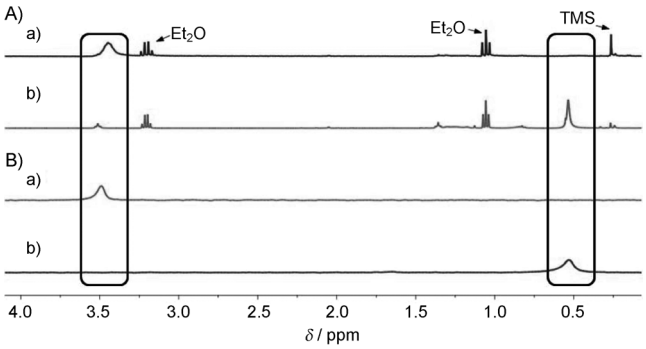


Figure 1. A) ^{1}HNMR spectra of a) [{(PPh$_3$)CuH}$_6$] and b) [{(PPh$_3$)CuH}$_6$] and BDP in a C_6D_6 solution. B) ^{2}H NMR spectra a) [{(PPh$_3$)CuD}$_6$] and b) [{(PPh$_3$)CuD}$_6$] and BDP in a C_6D_6 solution.

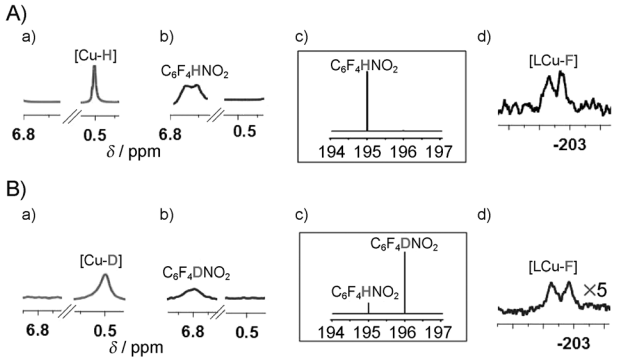


Figure 2. A) a) ^{1}H NMR spectra of a C_6D_6 solution of [{(PPh$_3$)CuH}$_6$] and BDP; b) ^{1}H NMR spectra, c) GC/MS, and d) ^{19}F NMR spectra of [{(PPh$_3$)CuH}$_6$] and BDP after addition of PFNB in a C_6D_6 solution. B) a) ^{2}H NMR spectra of the C_6H_6 solution of [{(PPh$_3$)CuD}$_6$] and BDP; b) ^{2}H NMR spectra, c) GC/MS, and d) ^{19}F NMR spectra of [{(PPh$_3$)CuD}$_6$] and BDP after addition of PFNB in a C_6H_6 solution.

coupling of the P atom with copper hydride (see Figure S5 in the Supporting Information). ^{31}PNMR spectroscopy performed in the temperature range 298–213 K in [D$_8$]THF confirmed that BDP and PPh_3 ligands (1:1) bound to copper (see Figures S6–S9 in the Supporting Information). Furthermore, ESI/MS spectra of the solution of [{(Ph$_3$P)CuH}$_6$] with BDP showed a peak at *m/z* 771.1584 D, which was assigned to [Cu(BDP)(PPh$_3$)]$^+$ (cal. 771.1561 D; Figure S10 in the Supporting Information). Thus, this copper hydride could be [Cu(BDP)H(PPh$_3$)]. It was feasible to investigate the stoichiometric reaction between copper hydride and PFNB.

The reactivity of copper hydride with PFNB was investigated by ^{1}H, ^{2}H, and ^{19}F NMR spectroscopy as well as GC/MS. Addition of 1 equivalent of PFNB to a solution of [{(Ph$_3$P)CuH}$_6$] and BDP in C_6D_6 resulted in the disappearance of the signal at $\delta = 0.51$ ppm within 10 minutes, and the appearance of a signal at $\delta = 6.73$ ppm, which is the H of 1,2,4,5-tetrafluoronitrobenzene (Figure 2 A a,b). More interestingly, the ^{19}F NMR spectra showed a new signal at $\delta = -202.4$ ppm, thus indicating the formation of a [Cu-F] intermediate (Figure 2 A d) according to previous reports.[14] Replacing [{(Ph$_3$P)CuH}$_6$] by [{(Ph$_3$P)CuD}$_6$] in the presence of BDP showed that the D was transferred to PFNB, as monitored by ^{2}H NMR spectroscopy (Figure 2 B a,b), and the [Cu-F] intermediate was also observed in the ^{19}F NMR spectrum. We used GC/MS to analyze the products and 80 % $C_6F_4DNO_2$ was detected (Figure 2 B c), and is consistent with 90 % [{(Ph$_3$P)CuD}$_6$] as the hydrogen source. Notably, the control experiment using [{(Ph$_3$P)CuH}$_6$] in the absence of BDP showed no HDF product but only aniline after reducing the nitro group of PFNB (see Figure S11 in the Supporting Information). The isotope effect of hydrogen sources was obtained (49 versus 17 %) by comparison of the yields of HDF products using [{(Ph$_3$P)CuH}$_6$] and [{(Ph$_3$P)CuD}$_6$] in the presence of BDP. These results strongly suggested that copper hydrides supported by BDP were able to react with the C–F bond and could be key intermediates.

There are several mechanisms for metal hydrides activating C–F bonds, including oxidative addition,[3a,4] electron transfer,[8b,15] and nucleophilic attack.[9,10,12a,g,16] According to the previous reports for the CuCl/KO*t*Bu and BDP/silane protocol,[11h,e] [(BDP)CuH] was proposed as active intermediate. Thus, to understand the reaction pathway, we carried out density functional theory (DFT) calculations (see the Supporting Information) starting from [(BDP)CuH] and the results are shown in Figure 3 A. From the initial loosely bound complex **A** involving [(BDP)CuH] and PFNB, the reaction of

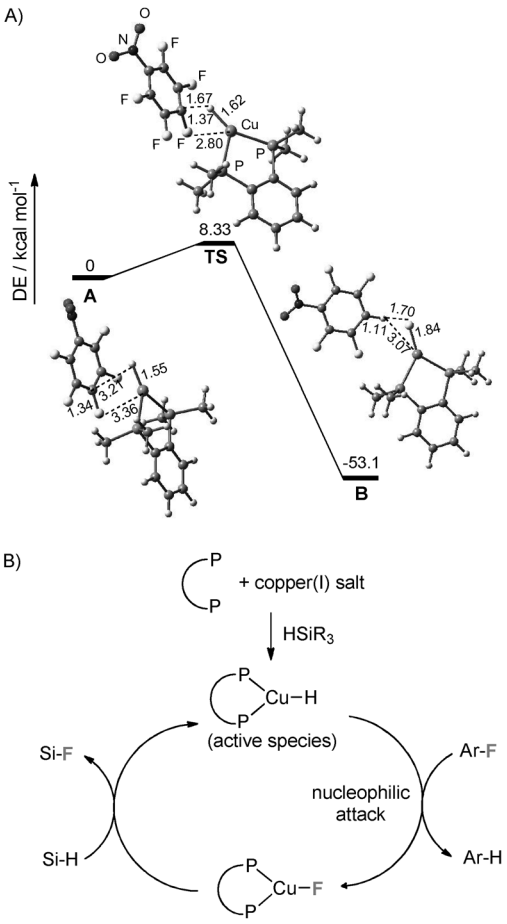


Figure 3. A) Computed reaction profile for HDF of PFNB by [(BDP)CuH]. B) Proposed catalytic cycle for copper-catalyzed HDF.

PFNB with copper hydride proceeds via the transition-state **TS** ($E = +8.33$ kcal mol^{-1}). The **TS** features a side-on orientation of PFNB, thus making the fluorine available to interact with the vacant site of copper center. The distance between the hydride and the *para*-C atom is shortened to 1.67 Å, together with an elongated *para*-C–F bond (1.37 Å). In contrast, the distance between Cu and the *para*-F atoms is shortened to 2.80 Å, together with an elongated Cu–H bond (1.62 Å). This data suggests the concerted nucleophilic attack on the C–F bond by [LCuH]. The total reaction goes through a highly favorable process ($\Delta E = -53.1$ kcal mol^{-1}) with a low barrier of 8.33 kcal mol^{-1}. This value is consistent with the fast HDF (10 min) between [(BDP)CuH] and PFNB at room temperature. We also attempted to explore other possible pathways such as oxidative addition,[7a] but could not optimize the plausible copper(III) intermediates or transition states. In addition, NBO charge analysis of [(BDP)CuH] showed that the charge of the hydride is -0.47 *e*, which is much larger than that of [Au(NHC)H] (-0.26 *e*).[5] This pronounced hydride character of [(BDP)CuH] also supports the mechanism for nucleophilic attack by copper hydride. Based on experimental and computational results, we illustrate the proposed catalytic cycle in Figure 3 B.

In summary, we have reported the first example of copper-catalyzed hydrodefluorination of fluoroarenes using silanes as a hydrogen source. Copper exhibited high reactivity and regioselectivity toward a broad scope of fluoroarenes. Moreover, copper hydrides were observed during catalytic process and the unprecedented reactivity toward C–F bonds has been demonstrated. Furthermore, DFT calculations suggest a mechanism for nucleophilic attack on the C–F bonds by the copper hydride. This work presents valuable insights for further studies using copper catalysts for C–F bond functionalization.

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