Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Guo, K. Bamford and D. W. Stephan, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB00912D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C9OB00912D

Journal Name

COMMUNICATION

9-Borabicyclo[3.3.1]nonane-induced Friedel–Crafts benzylation of arenes with benzyl fluorides

Jing Guo,[a] Karlee L. Bamford[a] and Douglas W. Stephan*[a]

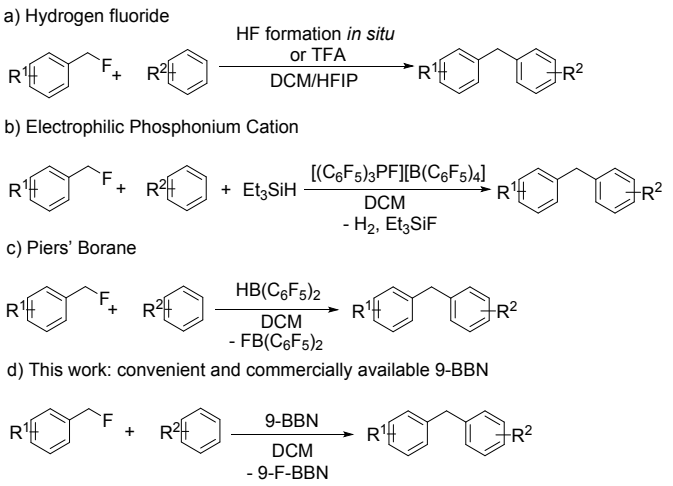
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Friedel–Crafts benzylation of arenes with benzyl fluorides using 9-borabicyclo[3.3.1]nonane (9-BBN) as a mediator has been developed. This provides a simple and cheap route to the activation of C-F bonds to synthesize 1,1-diarylmethanes in good to excellent yield (up to 98%) under mild conditions. Functional group tolerance and the mechanism are considered.

Carbon-fluorine bonds are among the strongest single bonds involving carbon and their selective activation and transformation under mild conditions remains a challenge.[1-13] Due to potential applications in synthetic organic chemistry and the prevalence of fluorinated environmental contaminants,[14-18] C-F bond activation has attracted the attention of organic, inorganic and organometallic chemists alike.[19-20] There have been a number of synthetic strategies developed for the use of benzyl fluorides in Friedel-Crafts benzylation (Scheme 1). In 2013, Kemnitz and co-workers reported heterogeneous C-F bond activation of benzyl fluoride and fluoromethane substrates using nanoscopic aluminium chlorofluoride (ACF) in the presence of Et_3SiH.[21] In 2014, Paquin *et al.* detailed the *in situ* generation of HF acid for benzyl fluoride activation promoted by HFIP (hexafluoro-2-propanol).[22] The Paquin group subsequently described an improved methodology using HFIP and the Brønsted acid trifluoroacetic acid (TFA) as an initiator for HF-promoted Friedel-Crafts benzylation from benzylic fluorides.[23-25] In 2016, our group described the coupling of benzyl fluorides with arenes and allylic silanes, catalysed by the electrophilic fluorophosphonium catalyst (EPC) $[(C_6F_5)_3PF][B(C_6F_5)_4]$, under mild conditions and with short reaction times.[26-27] In 2018, our group further reported that combination of hydridoboranes (e.g. catecholborane, pinacolborane, Piers' borane) and fluoroalkanes effected hydrodefluorination, dehydrofluorination, or boryldefluorination, without a catalyst.[28] These results demonstrated that the more highly electrophilic hydridoboranes were more reactive towards fluoroalkanes. Despite these advances, the development of Friedel–Crafts coupling reactions of arenes and benzyl fluorides *via* a practical and simple method remains a meaningful pursuit.



Scheme 1 Recent methods for C-F bond activation of benzyl fluorides in Friedel–Crafts reaction (TFA = trifluoroacetic acid, HFIP = hexafluoro-2-propanol).

In our previous work, we found that the cheap and commercially available hydridoborane 9-BBN can activate the C-F bonds of fluoroalkanes and a benzyl fluoride substrate. This borane represents an attractive alternative to more exotic boranes (e.g. $HB(C_6F_5)_2$), highly reactive Lewis acid catalysts (ACF, EPCs), or highly corrosive Brønsted acids (HF) for C-F bond activation. Herein, we describe the use of the readily available 9-BBN in Friedel–Crafts benzylation of arenes with benzyl fluorides. These reactions provide facile access to 1,1-diarylmethanes, offering a potential strategy to simple

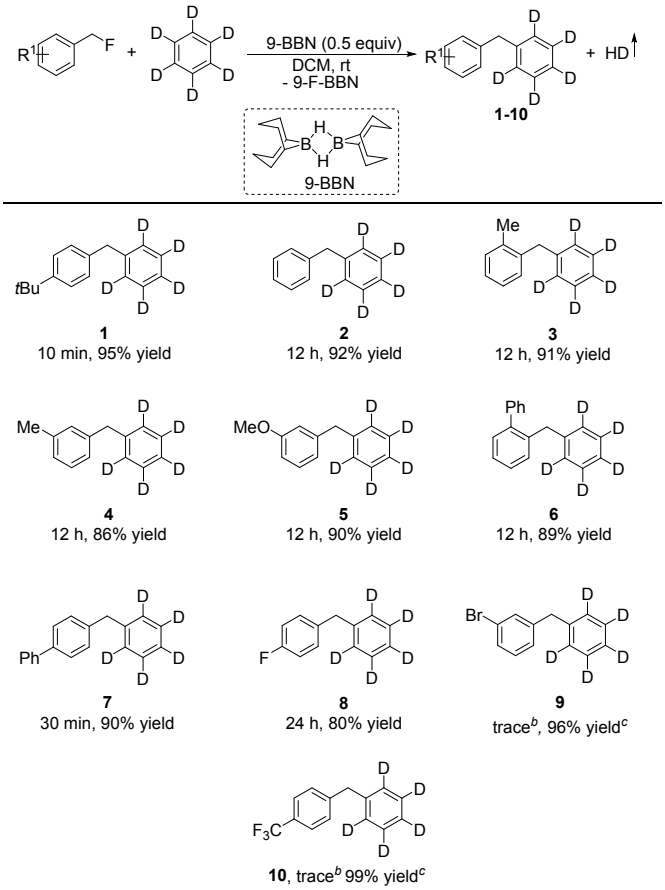
[a] Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada, E-mail: dstephan@chem.utoronto.ca

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C9OB00912D

synthetic building blocks reminiscent of those found in natural products and medicinal chemistry.[29-30]

Table 1 Reactions of benzyl fluorides with C_6D_6.[a]

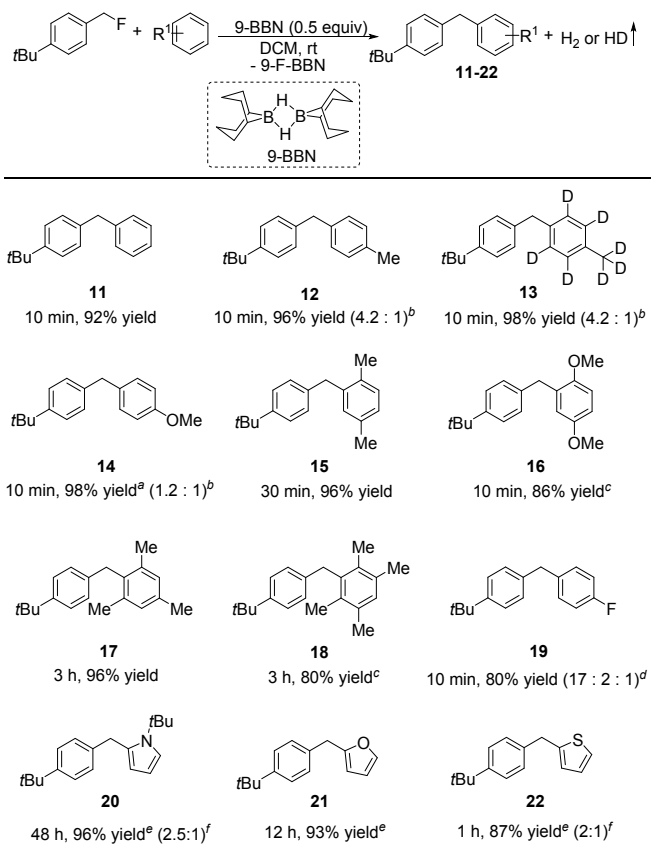


[a] All reactions were performed with benzyl fluorides (0.05 mmol, 1.0 equiv), excess C_6D_6 (0.2 mL) and 9-BBN dimer (0.025 mmol, 6.2 mg) in DCM (0.4 mL) at 25 °C for the specified reaction time. Isolated yield. [b] At 50 °C for 2 days. [c] Using $HB(C_6F_5)_2$ (0.05 mmol, 17.3 mg) instead of 9-BBN dimer.

The reactivity of benzyl fluorides with excess C_6D_6 in DCM solution in the presence of 0.5 equivalents of 9-BBN dimer was investigated (Table 1). Various electron-rich benzyl fluorides (R = 4-*t*Bu, H, 2-Me, 3-Me, 3-MeO, 2-Ph and 4-Ph) reacted to provide Friedel–Crafts benzylation resulting in the corresponding diarylmethanes **1–7** in good to excellent yield (80–95 %) in 10 minutes to 12 hours at room temperature. At the same time, the bubbling of HD was observed, and 9-F-BBN was detected by ^{19}F and ^{11}B NMR spectroscopy as one of by-products (see ESI). The position of the substituents on the benzyl fluoride appear to have no effect on the yield of this reaction. Substitution of the benzyl fluoride with a weakly electron-withdrawing substituent (4-fluoro **8**) slowed the observed reactivity and lead to significantly longer reaction times. Interestingly, almost no reaction was observed when more electron-deficient benzyl fluorides (3-bromo **9**, 4-trifluoromethyl **10**) were used. Only traces of the anticipated products were seen and even upon raising the reaction temperature to >50 °C, the benzyl fluoride starting materials persisted. In contrast, use of the more electrophilic borane $HB(C_6F_5)_2$ in place of 9-BBN led to complete reaction of these deactivated benzyl fluoride substrates.

The corresponding reactivity of arenes with 4-*tert*-butyl benzyl fluoride was also surveyed (Table 2). The Friedel–Crafts reaction of benzyl fluorides with benzene or electron-rich arenes (toluene, toluene-d_8, anisole, *p*-xylene, 1,4-dimethoxybenzene, mesitylene, 1,2,4,5-tetramethylbenzene) in the presence of 9-BBN dimer (0.5 equiv) proceeded in 10 minutes to 3 hours at room temperature. These reactions afforded the corresponding diarylmethanes (**11–18**) in good to excellent yields (80–98 %). The ratio of regioisomers was determined by ^1H NMR spectroscopic analysis. In the case of the electron-deficient fluorobenzene, the reaction afforded three isomers of the products **19** in 80% yield and 17:2:1 ratio for the *para*-, *ortho*- and *meta*-fluoro-substituted products. The desired Friedel–Crafts benzylated products were not observed when deactivated electron-deficient arenes (1,2-difluorobenzene, and 1,2-dichlorobenzene) were used. In these instances, only polymerization of benzyl fluoride was observed. However, the corresponding Friedel-Crafts reactions with heterocycles 1-*tert*-butyl-1*H*-pyrrole, furan and thiophene proceeded smoothly, affording the corresponding products **20–22** in good yields (90–96%).

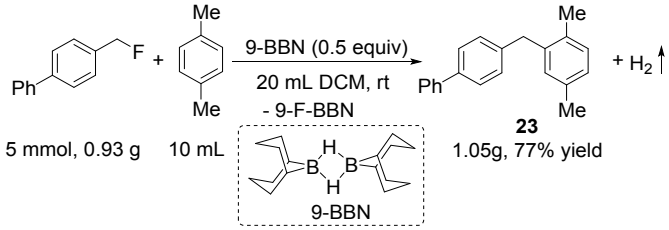
Table 2 Reactions of *tert*-butylbenzyl fluorides with arenes and heterocycles.[a]



[a] All reactions were performed with 1-(*tert*-butyl)-4-(fluoromethyl)benzene (0.05 mmol, 1.0 equiv), excess arene (0.2 mL) and 9-BBN dimer (0.025 mmol, 6.2 mg) in DCM (0.4 mL) at 25 °C for the specified reaction time. Isolated yield. [b] Ratio of the *para: ortho* isomers. [c] 1-(*tert*-Butyl)-4-(fluoromethyl)benzene (0.05 mmol, 1.0 equiv) and arene (1.1 equiv). [d] Ratio of the *para: ortho: meta* isomers. [e] 1-(*tert*-Butyl)-4-(fluoromethyl)benzene (0.05 mmol, 1.0 equiv) and arene (0.1 mL). [f] Ratio of the 2-: 3-isomers.

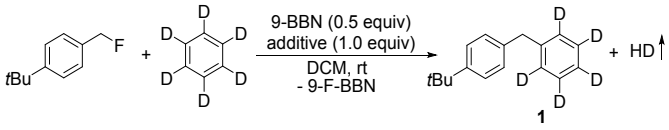
DOI: 10.1039/C9OB00125D

These facile Friedel-Crafts reactions were shown to be viable on a gram-scale. To this end, 4-(fluoromethyl)-1,1'-biphenyl (0.93 g, 5.0 mmol) was reacted with *p*-xylene (10 mL) In the presence of 9-BBN dimer (0.62 g, 2.5 mmol), to give the product $PhC_6H_4CH_2(C_6H_3Me_2)$ **23** (1.05 g, 77% yield) as a white solid (Scheme 2).



Scheme 2 Gram-scale synthesis of **23**.

Table 3 Examining functional group compatibility.



Entry[a]	Additive	Yield of **1** [b]
1	-	95 [c]
2	Et_3SiH	88
3	PhC≡N	84
4	Ph_2CO	75
5	PhC≡CPh	74
6	PhC≡CH	65
7	Ph_3N	68
8	$Ph_2C{=}CH_2$	66
9	C_6H_{10} (cyclohexene)	62
10	$TMSCF_3$	73
11	$PhCF_3$	69
12	Me_3SiOPh	66
13	Ph_2NH	56
14	Ph_2O	56
15	PhOH	42
16	PhCH=NPh	33
17	P(*o*-MeC_6H_4)$_3$	23
18	$PhC(O)N(H)CH_2Ph$	10
19	$PhNH_2$	0
20	C_5H_5N	0
21	C_5H_5NO	0
22	H_2O	0
23	Ph_3PO	0
24	Ph_3COH	0

[a] The standard reaction was done in the presence of 1.0 equiv of the given additive. [b] GC-MS yields were determined after a 24 h reaction time using diphenylmethane as standard. [c] Isolated yield.

To probe the functional group tolerance of this methodology, a standard reaction was investigated in the presence of additives incorporating various functional groups. Our group[31] as well as that of Glorius[32] have exploited this screening method in the past. The reaction of *p*-*t*Bu$C_6H_4CH_2F$ with C_6D_6 mediated by 9-BBN dimer, which gave the product **1** in 95% isolated yield (Table 3, entry 1), was used as the model. Generally, while the yields diminish to some extent, the benzylation reaction is tolerant of the presence of triethylsilane, nitrile, ketone, alkyne, tertiary amine, olefin, CF_3-species and silylether (Table 3, entries 1–12). The yields are further reduced to less than 60% in the presence of secondary amine, phenol, imine, phosphine or amide (Table 3, entries 13–18). Lewis basic additives such as aniline, pyridine, pyridine N-oxide, water, phosphine-oxide or alcohol precluded the benzylation completely (Table 3, entries 19–24), presumably as a result of coordination of such donors to 9-BBN. The catalyst-free dehydrocoupling of 9-BBN and protic species, such as amines and alcohols, has been previously described.[33]

The mechanism of these benzylation is thought to be related to that proposed in our previous studies of C-F bond hydrodefluorination.[28] In that case, computations revealed that $HB(C_6F_5)_2$ interacts with the C-F bond to generate a benzyl-cation hydridofluoroborate anion pair which is quenched by arene. The arenium cation subsequently releases proton and H_2 is generated upon its combination with the hydridofluoroborate anion. In the present case, similar generation of the benzyl cation by 9-BBN prompts Friedel–Crafts chemistry and affords the diarylmethane products with liberation of H_2. Support for this reaction pathway were derived from NMR spectroscopy. While the evolution of HD in the formation is visible (see SI), the corresponding ^1H and $^2H\{^1H\}$ NMR resonances were also observed ($\delta(^1H)$: 4.37 (1:1:1, t) ppm; $\delta(^2H\{^1H\})$: 4.5 (s) ppm). Similarly, the formation of 9-F-BBN was affirmed by ^{19}F NMR and ^{11}B NMR spectra ($\delta(^{19}F)$: -46.9 ppm; $\delta(^{11}B)$: 63.9 ppm). Interesting, multinuclear NMR spectroscopy reveals the liberation of HD is subsequent to the formation of the diarylmethane. We speculate that the protic arenium cation reacts with the transient anion, $[FHBBN]^-$ to give initially the kinetic product of B-C bond cleavage, which gradually releases HD yielding the thermodynamically favoured 9-F-BBN (see ESI). While this use of 9-BBN provides a facile avenue to diarylmethane product formation, we note that it is insufficiently Lewis acidic to activate the electron-deficient benzyl fluorides, whereas the more Lewis acidic $HB(C_6F_5)_2$ is effective.

Conclusions

In summary, we have reported a simple and cheap strategy for the activation of C-F bonds affording the Friedel–Crafts benzylation of arenes with benzyl fluorides. A variety of 1,1-diarylmethanes were obtained in good to excellent yield under these mild reaction conditions and the method was amenable to larger, gram-scale reactions. Thus, this is an attractive and simple protocol for the preparation of various 1,1-diarylmethanes from benzyl fluorides using a commonly available and easy to handle borane, 9-BBN. We are continuing to explore the utility of main group catalysts for applications in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

NSERC of Canada is thanked for financial support. D.W.S is grateful for the award of a Canada Research Chair and a Visiting Einstein Fellowship at TU Berlin. K.L.B is grateful for the award of an NSERC CGS-D scholarship. The authors thank Prof. Sophie Rousseaux and Nick Michel (University of Toronto) for assistance with GC-MS.

Notes and references

1. J. Burdeniuc, B. Jedlicka and R. H. Crabtree, *Chem. Ber.* , 1997, **130**, 145-154.
2. S. J. Blanksby and G. B. Ellison, *Acc. Chem. Res.*, 2003, **36**, 255-263.
3. G. Meier and T. Braun, *Angew. Chem. Int. Ed.*, 2009, **48**, 1546-1548.
4. H. Amii and K. Uneyama, *Chem. Rev.* , 2009, **109**, 2119-2183.
5. E. Clot, O. Eisenstein, N. Jasim, S. A. MacGregor, J. E. McGrady and R. N. Perutz, *Acc. Chem. Res.*, 2011, **44**, 333-348.
6. W. D. Jones, *Dalton Trans.*, 2003, 3991.
7. H. Torrens, *Coord. Chem. Rev.*, 2005, **249**, 1957.
8. A. D. Sun, *Dalton Trans.*, 2010, **39**, 10362.
9. J. A. Love, T. Braun and F. Wehmeier, *Eur. J. Inorg. Chem.*, 2011, 613.
10. L. Keyes, A. D. Sun and J. A. Love, *Eur. J. Org. Chem.*, 2011, 3985.
11. J.-F. Paquin, *Synlett.*, 2011, 289.
12. T. Stahl, H. F. T. Klare and M. Oestreich, *ACS Catal.*, 2013, 1578–1587.
13. J. D. Hamel and J. F. Paquin, *Chem. Comm.*, 2018, **54**, 10224-10239.
14. G. Theodoridis, in *Advances in Fluorine Science*, ed. A. Tressaud, Elsevier, 2006, vol. 2, pp. 121–175.
15. T. Fujiwara and D. O'Hagan, *J. Fluorine Chem.*, 2014, **167**, 16.
16. J. Wang, M. Sánchez-Roselló, J. Aceña, C. d. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432.
17. E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315.
18. M. Braun and J. Eicher, in *Modern Synthesis Processes and Reactivity of Fluorinated Compounds*, eds. H. Groult, F. R.Leroux and A. Tressaud, Elsevier,, 2017, pp. 7–25.
19. J. L. Kiplinger, T. G. Richmond and C. E. Osterberg, *Chem. Rev.* , 1994, **94**, 373-431.
20. Y. Zhu, J. L. Han, J. D. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho and F. D. Toste, *Chem. Rev.*, 2018, **118**, 3887.
21. M. Ahrens, G. Scholz, T. Braun and E. Kemnitz, *Angew. Chem. Int . Ed.*, 2013, **52**, 5328-5332.
22. P. A. Champagne, Y. Benhassine, J. Desroches and J. F. Paquin, *Angew. Chem. Int. Ed.*, 2014, **53**, 13835-13839.
23. J.-F. Paquin, J.-D. Hamel, M. Beaudoin and M. Cloutier, *Synlett*, 2017, **28**, 2823-2828.
24. R. Hemelaere, P. A. Champagne, J. Desroches and J.-F. Paquin, *J. Fluorine Chem.*, 2016, **190**, 1
25. N. S. Keddie, P. A. Champagne, J. Desroches, J.-F. Paquin and D. O'Hagan, *Beilstein J. Org. Chem.*, 2018, **14**, 106.
26. J. Zhu, M. Pérez, C. B. Caputo and D. W. Stephan, *Angew. Chem. Int . Ed.*, 2016, **55**, 1417-1421.
27. J. T. Zhu, M. Pérez and D. W. Stephan, *Angew. Chem. Int . Ed.*, 2016, **55**, 8448-8451.
28. K. L. Bamford, S. S. Chitnis, Z.-w. Qu and D. W. Stephan, *Chem. Eur. J.*, 2018, **24**, 16014.
29. S. Mondal and G. Panda, *RSC Adv.*, 2014, **4**, 28317-28358.
30. M. W. P. Bebbington, *Chem. Soc. Rev.*, 2017, **46**, 5059.
31. D. W. Stephan, S. Greenberg, T. W. Graham, P. Chase, J. J. Hastie, S. J. Geier, J. M. Farrell, C. C. Brown, Z. M. Heiden, G. C. Welch and M. Ullrich, *Inorg. Chem.*, 2011, **50**, 12338–12348.
32. K. D. Collins and F. Glorius, *Nat. Chem.*, 2013, **5**, 597.
33. E. A. Romero, J. L. Peltier, R. Jazzar and G. Bertrand, *Chem. Commun.*, 2016, **52**, 10563-10565.

Journal Name COMMUNICATION

View Article Online
DOI: 10.1039/C9OB00912D

TOC

9-borabicyclo[3.3.1]nonane dimer (9-BBN) mediates the Friedel–Crafts benzylation of arenes with benzyl fluorides, affording a series of 1,1-diarylmethanes under mild conditions.