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Rapid access to diverse, trifluoromethyl-substituted alkenes using complementary strategies†

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Two synergistic approaches to the facile assembly of complex α-trifluoromethyl alkenes are described. Using α-trifluoromethyl-β-silyl alcohols as masked trifluoromethyl alkenes, cross-coupling or related functionalization processes at distal electrophilic sites can be executed without inducing Peterson elimination. Subsequent Lewis acidic activation affords functionalized α-trifluoromethyl alkenes. Likewise, the development of a novel α-trifluoromethylvinyl trifluoroborate reagent complements this approach and allows a one-step cross-coupling of (hetero)aryl halides to access a broad array of complex α-trifluoromethyl alkenes.

Introduction

The ability of fluorine to modulate the pharmacological properties of biologically active molecules and to improve metabolic stability has spurred the development of an array of synthetic methods for both incorporation and modification of fluorinated motifs within complex molecular settings.[1] Of interest are α-trifluoromethyl alkenes, for they are known peptide isosteres,[2] are medicinally relevant moieties in pharmacologically active compounds,[3] and are synthetic intermediates to other fluorinated species[4] (Scheme 1). For instance, cyclopropanation yields trifluoromethyl-substituted cyclopropanes, which are established *tert*-butyl isosteres,[5a] and radical defluorinative alkylation gives 1,1-*gem*-difluoroalkenes, which are proposed ketone mimics.[5b–e] Although several routes for preparing α-trifluoromethyl alkenes are reported, they are frequently lacking in functional group compatibility or ease of operation. Current approaches for the synthesis of this motif fall under three categories: (1) Wittig-type methylenation of trifluoromethyl ketones (TFMKs) under strongly basic conditions;[6] (2) Suzuki, Negishi, and Kumada cross-couplings that employ an arylboron species and highly volatile bromo-3,3,3-trifluoroprop-1-ene;[7] (3) Peterson-type olefination of TFMKs that utilizes a Grignard reaction in its synthetic sequence, thus limiting protic group tolerance.[8]
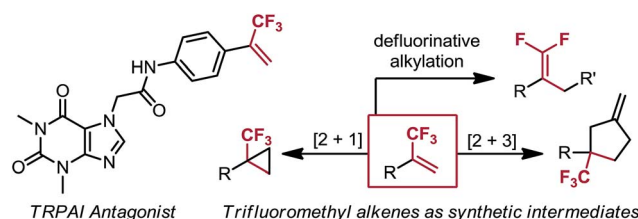
As part of a program to access functionalized fluorinated motifs, we became interested in efficient routes to α-

trifluoromethyl alkenes that were both structurally complex and functionally diverse. Two complementary strategies were envisioned: (1) employment of cores with α-trifluoromethyl-β-silyl alcohols as "masked" trifluoromethyl alkenes, thus allowing molecular complexity to be installed without incurring undesired side reactions of the alkene; (2) utilization of a solid, bench-stable organotrifluoroborate reagent for rapid, late-stage introduction of the 3,3,3-trifluoro-1-propenyl motif (Scheme 2). This reagent eliminates the use of a volatile compound with limited bench-stability in favor of a crystalline, bench-stable solid that can be readily synthesized on a multigram scale and provides access to an umpolung bond disconnection. Additionally, the use of aryl bromides rather than arylboron species offers improvement on the availability and cost of starting materials.

Results and discussion

Functionalization of masked α-CF₃ alkenes

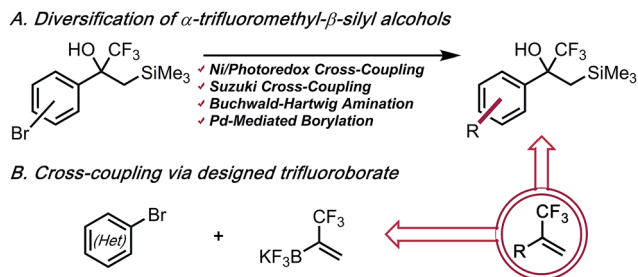α-Trifluoromethyl-β-silyl alcohols were reported recently by Leadbeater and co-workers as viable precursors to

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Scheme 1 α-Trifluoromethyl alkenes in a pharmaceutically active compound and as synthetic intermediates.

A. Diversification of α-trifluoromethyl-β-silyl alcohols

✓ Ni/Photoredox Cross-Coupling
✓ Suzuki Cross-Coupling
✓ Buchwald–Hartwig Amination
✓ Pd-Mediated Borylation

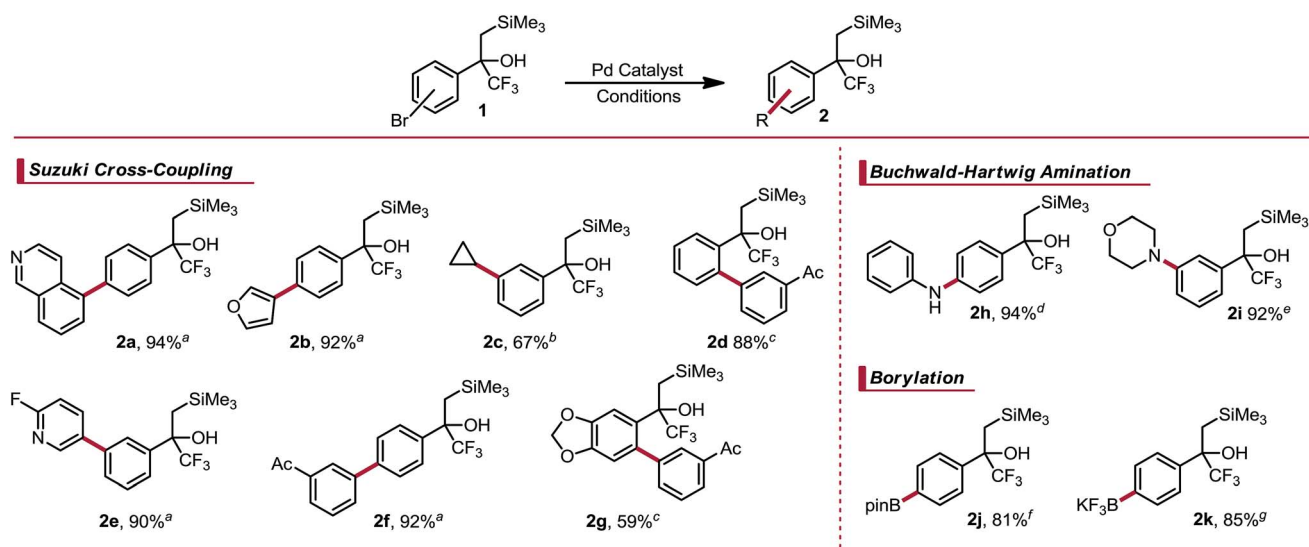*B. Cross-coupling via designed trifluoroborate*

Scheme 2 α-Trifluoromethyl alkenes *via* two complementary approaches.

α-trifluoromethyl alkenes.[8] The scope of this approach was hampered by the lengthy synthetic sequence used to prepare each example and the general intolerance of their approach toward Lewis or Brønsted acidic functional groups. However, α-trifluoromethyl-β-silyl alcohols were noted to be surprisingly stable despite the known propensity of tertiary β-silyl alcohols to undergo spontaneous elimination under both weakly acidic or basic conditions.[9] The origin of this stability is likely derived from electronic deactivation and steric shielding by the α-trifluoromethyl group. We imagined that these α-trifluoromethyl-β-silyl alcohols could serve as masked CF$_3$ alkenes, which would enable rapid diversification to assemble species that would not only be incompatible with the original sequence, but also give rise to α-trifluoromethyl alkenes that would be otherwise challenging, if not impossible, to prepare. Indeed, we envisioned that we could further elaborate these

substructures by executing C$_{sp^2}$–C$_{sp^3}$ photoredox cross-coupling,[10] Suzuki cross-coupling,[11] Buchwald–Hartwig amination,[12] and palladium-mediated borylation.[13] After functionalization, the relatively mild nature of dehydrative elimination would furnish structurally complex α-trifluoromethyl alkenes. The amenability of α-trifluoromethyl-β-silyl alcohols toward Suzuki–Miyaura coupling was first investigated. Three regioisomeric, brominated cores were prepared and subjected to cross-coupling with aryl trifluoroborates. Good reactivity without concomitant olefination was observed. The *para-* and *meta*-substituted aryl bromides coupled in high yield with aryl- and heteroaryl trifluoroborates under relatively standard conditions (Table 1).[14] C$_{sp^2}$–C$_{sp^3}$ Cross-coupling using potassium cyclopropyltrifluoroborate also proceeded well using standard conditions.[15a] The steric bulk of the α-trifluoromethyl-β-silyl moiety initially impeded coupling of the *ortho*-substituted aryl bromide core. Using high throughput experimentation (HTE),[15b] suitable conditions for *ortho*-coupling were quickly identified (see ESI† for details on HTE studies). Electron rich, sterically bulky phosphine ligands were the most efficacious, with 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene (QPhos) proving optimal. Using these conditions, cross-coupling proceeded smoothly to afford the *ortho*-arylated structure **2d**. These conditions could also be extended to a dioxolane core **2g**.

Amination of these aryl bromides proceeded smoothly with both aniline and morpholine, providing the corresponding products (**2h** and **2i**) in high yield. The latter emphasizes the utility of these α-trifluoromethyl-β-silyl alcohols as masked

Table 1 Palladium-catalyzed cross-couplings of α-trifluoromethyl-β-silyl alcohols

Suzuki Cross-Coupling

2a, 94%[a] **2b**, 92%[a] **2c**, 67%[b] **2d** 88%[c]

2e, 90%[a] **2f**, 92%[a] **2g**, 59%[c]

Buchwald-Hartwig Amination

2h, 94%[d] **2i** 92%[e]

Borylation

2j, 81%[f] **2k**, 85%[g]

[a] Reaction conditions: Pd(OAc)$_2$ (1 mol%), RuPhos (3 mol%), organotrifluoroborate (1.1 equiv.), Na$_2$CO$_3$ (2 equiv.), EtOH (0.18 M), 85 °C, 24 h. [b] Reaction conditions: XPhos Pd G2 (3 mol%), organotrifluoroborate (1.2 equiv.), K$_2$CO$_3$ (3 equiv.), 10 : 1 CPME/H$_2$O (0.25 M), 100 °C, 24 h. [c] Reaction conditions: Pd(OAc)$_2$ (5 mol%), QPhos (12 mol%), organotrifluoroborate (1.1 equiv.), K$_2$CO$_3$ (2 equiv.), 2 : 1 dioxane/H$_2$O (0.25 M), 85 °C, 24 h. [d] Reaction conditions: XPhos Pd G2 (2 mol%), aniline (3 equiv.), Cs$_2$CO$_3$ (1.4 equiv.), PhMe (0.5 M), 100 °C, 24 h. [e] Reaction conditions: XPhos Pd G2 (2 mol%), morpholine (3 equiv.), Cs$_2$CO$_3$ (2.5 equiv.), 5 : 1 PhMe/tBuOH (0.42 M), 80 °C, 12.5 h. [f] Reaction conditions: XPhos Pd G2 (2 mol%), B$_2$pin$_2$ (3 equiv.), KOAc (3 equiv.), dioxane (0.5 M), 110 °C, 2 h. [g] Reaction conditions: XPhos Pd G2 (0.5 mol%), XPhos (1 mol%), BBA (3 equiv.), KOAc (3 equiv.), EtOH (0.1 M), 80 °C then KHF$_2$ (6.75 equiv.), MeOH (0.1 M).

trifluoromethyl alkenes, given the propensity of trifluoromethyl alkenes to undergo defluorinative amination under basic conditions.[16]

Although numerous arylboron species are commercially available, there is a paucity when compared to commercially available aryl halides. One could envision borylating trifluoroalkenyl-substituted aryl bromides, but this approach is complicated by the facile defluorinative borylation of trifluoromethyl alkenes, resulting in 1,1-*gem*-difluoroalkenes.[17] Consequently, we were interested in the borylation of these masked trifluoromethyl alkenes to generate arylboron species capable of serving as points for further diversification. Palladium-catalyzed borylation using either bis(pinacolato) diboron[18] or bisboronic acid (BBA)[19] occurred efficiently and in good yield to provide access to arylboronic ester **2j** and aryltrifluoroborate **2k** (Table 1). Notably, treatment of the intermediate boronic acid obtained from the BBA approach with excess KHF$_2$ induced no observable Peterson elimination. This is a testament to the stability of the masking motif, given that both fluoride-induced and weakly Lewis acid-induced elimination pathways are known with β-silyl alcohols.[9b,20] Arylboron species **2j** and **2k** were effective cross-coupling substrates, reacting in good yield with 5-bromoindole and 7-bromo-3-fluoroquinoline to give the products **2l** and **2m**, respectively (Scheme 3).

Given the difficulty observed when attempting to prepare C$_{sp^2}$–C$_{sp^3}$ linkages using two-electron manifolds,[21] Ni/photoredox dual catalytic processes were next examined. This approach is convenient for C$_{sp^2}$–C$_{sp^3}$ cross-coupling within complex molecular settings because it can be executed under mild conditions and displays broad functional group tolerance.[10] A key feature of these methods is the use of carbon-centered radicals to enable room temperature transmetalation. As such, certain moieties that are prone to radical chemistry will engage in off-cycle reactions. For example, trifluoromethyl alkenes are known to undergo facile radical defluorinative alkylation, likely precluding them from this form of catalysis.[5b–d] Indeed, we conducted competition experiments and found alkylation of the alkene to be competitive with Ni-catalyzed cross-coupling (see ESI† for experimental details).
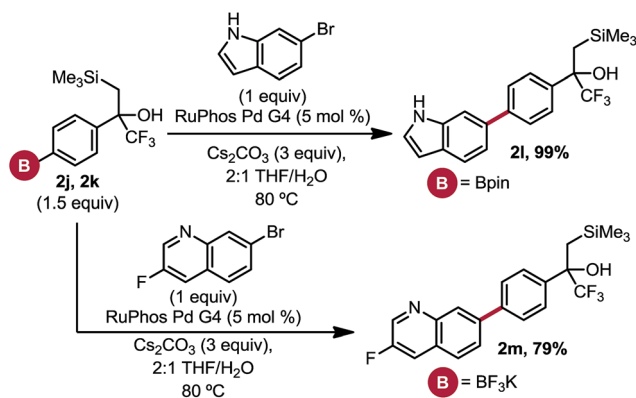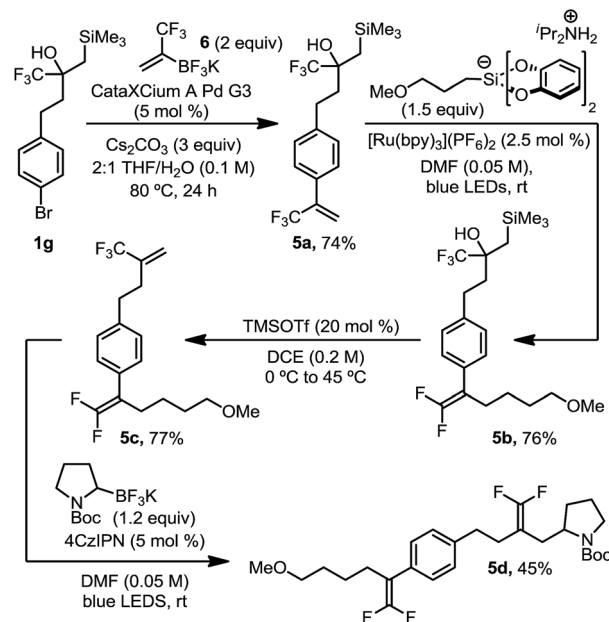
Scheme 4 Orthogonal introduction and reaction of α-trifluoromethyl alkenes. All yields are isolated yields after purification. For details, see the ESI.†

Thus, this reaction class is ideal for demonstrating α-trifluoromethyl-β-silyl alcohols as masked trifluoromethyl alkenes. Dual catalytic cross-coupling was initially investigated using secondary organotrifluoroborates and these brominated, masked alkenes.[22] Selection of the appropriate additive was crucial in achieving good reactivity. Carbonates and other basic additives, which are typically employed in C$_{sp^2}$–C$_{sp^3}$ couplings involving organotrifluoroborates, provided only partial conversion. Hypothesizing that the basic additive may deprotonate the relatively acidic α-trifluoromethyl alcohol present in the aryl bromide, we examined alternative additives to sequester the BF$_3$ generated upon oxidative fragmentation of the organotrifluoroborate. KF was identified as the most effective additive, enabling the C$_{sp^2}$–C$_{sp^3}$ cross-coupled products to be obtained in good yield (Table 2(A)). Success here is again remarkable because: (1) BF$_3$ can catalyze Peterson elimination[23] and (2) KF can be used despite the high fluorophilicity of silicon. Other radical precursors could also be utilized. Alkyl bis(catecholato) silicates coupled in good yield with brominated, masked trifluoromethyl alkenes, although higher catalyst loadings were required to achieve complete conversion in a timely manner (Table 2(B)).[24] Simple aryl masked trifluoromethyl alkenes, in addition to more complex *meta*-chloro (**2r**) and pyridyl (**2s** and **2t**) examples, cross-coupled in good yield. Ni/photoredox catalyzed thioarylation was also possible (**2t**).[25]

To demonstrate the full potential of this strategy for diversification, unmasking of the functionalized α-trifluoromethyl-β-silyl alcohols using trimethylsilyl trifluoro-methanesulfonate (TMSOTf) was explored. Although it proceeded smoothly for most substrates, a major challenge was conducting the Peterson elimination in the presence of Lewis basic sites. We found that elimination can be accomplished for some of the more

Scheme 3 Suzuki cross-coupling of borylated α-trifluoromethyl-β-hydroxy alcohols. All yields are isolated yields after purification. For details, see the ESI.†
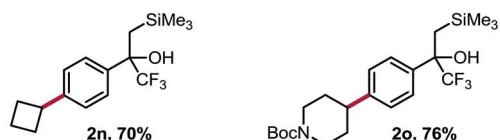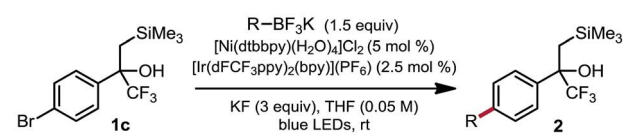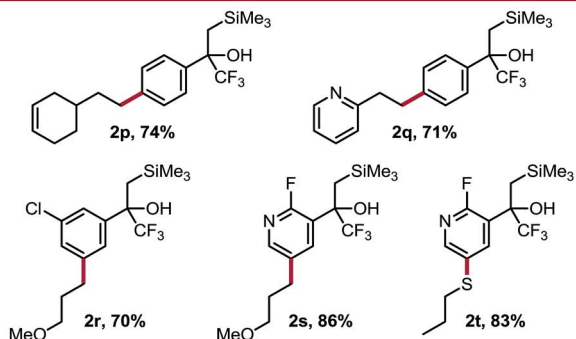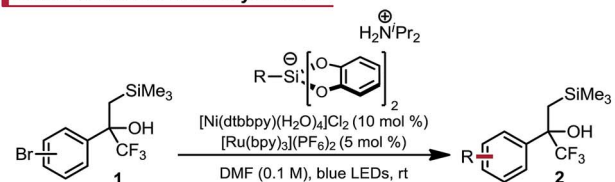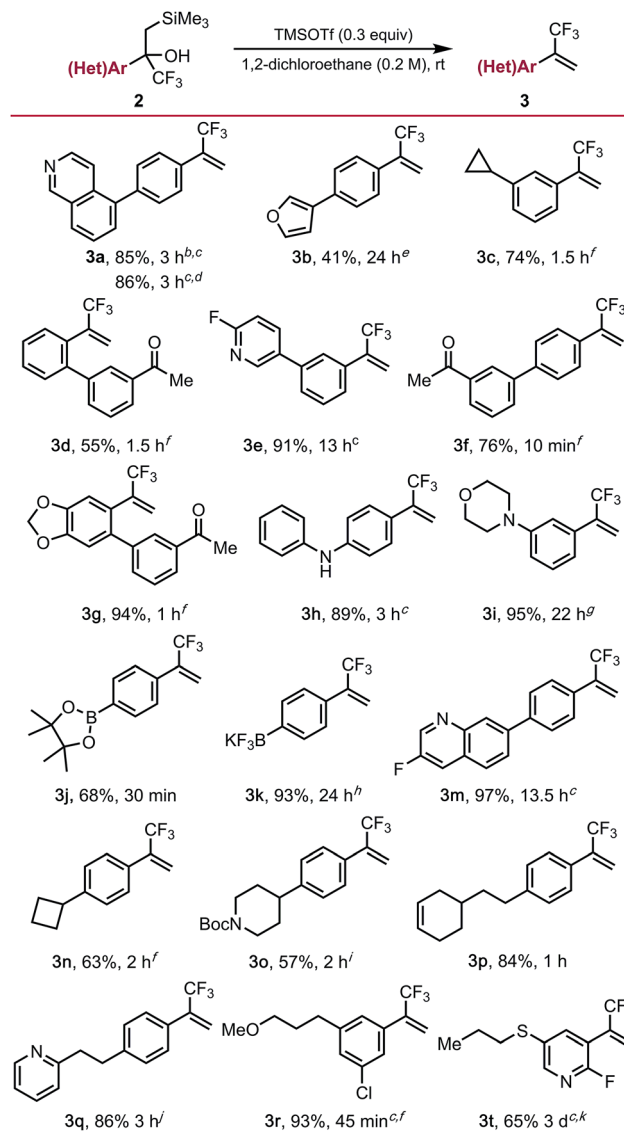
Table 2 Ni/Photoredox dual catalytic cross-coupling of masked trifluoromethyl alkenes[a]

A: Ni/Photoredox with Organotrifluoroborates

R–BF₃K (1.5 equiv)
[Ni(dtbbpy)(H₂O)₄]Cl₂ (5 mol %)
[Ir(dFCF₃ppy)₂(bpy)](PF₆) (2.5 mol %)
KF (3 equiv), THF (0.05 M)
blue LEDs, rt

2n, 70%   2o, 76%

B: Ni/Photoredox with Alkylsilicates

[Ni(dtbbpy)(H₂O)₄]Cl₂ (10 mol %)
[Ru(bpy)₃](PF₆)₂ (5 mol %)
DMF (0.1 M), blue LEDs, rt

2p, 74%   2q, 71%   2r, 70%   2s, 86%   2t, 83%

[a] All yields are isolated yields after purification. For details, see the ESI.

Table 3 α-Trifluoromethyl alkenes *via* Peterson elimination of cross-coupled products[a]

TMSOTf (0.3 equiv)
1,2-dichloroethane (0.2 M), rt

3a, 85%, 3 h[b,c]   86%, 3 h[c,d]
3b, 41%, 24 h[e]
3c, 74%, 1.5 h[f]
3d, 55%, 1.5 h[f]
3e, 91%, 13 h[c]
3f, 76%, 10 min[f]
3g, 94%, 1 h[f]
3h, 89%, 3 h[c]
3i, 95%, 22 h[g]
3j, 68%, 30 min
3k, 93%, 24 h[h]
3m, 97%, 13.5 h[c]
3n, 63%, 2 h[f]
3o, 57%, 2 h[i]
3p, 84%, 1 h
3q, 86% 3 h[j]
3r, 93%, 45 min[c,f]
3t, 65% 3 d[c,k]

[a] Elimination to α-trifluoromethyl alkenes. General reaction conditions: α-trifluoromethyl-β-silyl alcohol (1.0 equiv.), 1,2-dichloroethane (0.2 M), TMSOTf (0.3 equiv.), rt. All yields are isolated yields after purification. Some substrates required additional TMSOTf or increased reaction temperature, for additional details see the ESI. [b] Using 1.3 equiv. TMSOTf. [c] Conducted at 90 °C. [d] Conducted using 1.0 equiv. of HCl and 0.6 equiv. of TMSOTf. [e] Using 0.1 equiv. TMSOTf. [f] Using 0.2 equiv. TMSOTf. [g] Using 0.9 equiv. TMSOTf. [h] Using 2.0 equiv. TMSOTf. [i] Using 2.2 equiv. TMSOTf. [j] Using 1.2 equiv. TMSOTf. [k] Using 6.0 equiv. TMSOTf.

recalcitrant substrates if a super-stoichiometric amount (1.3 equiv.) of TMSOTf are employed (*e.g.*, isoquinoline **3a** [Table 3]). Alternatively, the addition of an equivalent of HCl to protonate the basic site (*e.g.*, the nitrogen of **2a**) enables successful elimination using sub-stoichiometric amounts (0.6 equiv.) of TMSOTf. Substrates containing less basic amines (**3e**, **3h**, **3m**) readily underwent elimination using catalytic amounts of TMSOTf, supporting the hypothesis of Lewis base-mediated deactivation of TMSOTf. Substrates containing ketone (**3d**, **3f**, **3g**), alkene (**3p**), strained rings (**3c**, **3n**), alkyl ether (**3r**), morpholine (**3i**), and acid sensitive furan (**3b**) functional groups underwent elimination in moderate to good yields. Unfortunately, while unmasking of free indole substrate **2l** was successful, undesired side reactions were observed on the indole moiety. Elimination proceeded smoothly in the presence of an N-Boc piperidine (**3o**), although reprotection of the free amine was required upon reaction completion. Unmasking of α-trifluoromethyl-β-silyl alcohol **2t** required additional TMSOTf and extended reaction times due to deactivation of the alcohol toward elimination by the electron-deficient 2-fluoropyridine core. Related alcohol **2s** was resistant toward elimination, only

undergoing partial conversion to the trifluoromethyl alkene even under rather forcing conditions. Interestingly, boronic ester **2j** and potassium organotrifluoroborate **2k** were also compatible with the Peterson elimination conditions. However, in the case of the latter, exposure of **3k** to KHF₂ upon reaction completion was required to return all the material to the trifluoroborate salt due to concomitant silyl-mediated defluorination.
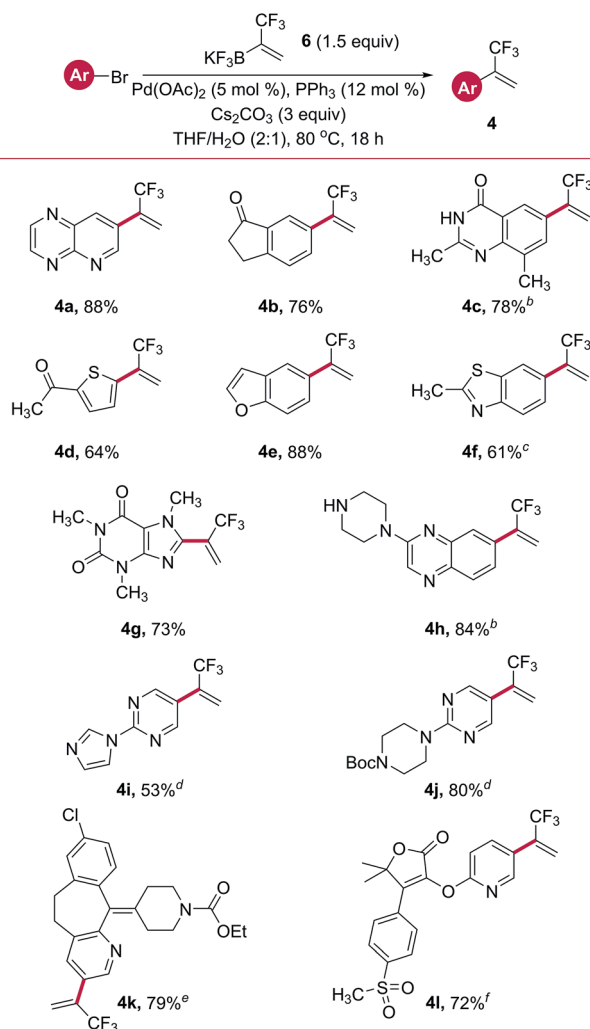
Direct access to α-trifluoromethyl alkenes using potassium trifluoromethylvinyl trifluoroborate

Direct, one-step Suzuki cross-coupling of potassium tri-fluoromethylvinyl trifluoroborate **6** with a host of aryl and heteroaryl bromides was next pursued. Initial success was found when using Pd(OAc)$_2$ with PPh$_3$ as a ligand (Table 4). Several aryl- and heteroaryl bromides containing a wide variety of functional groups were successfully cross-coupled, including a pyrido[2,3-*b*] pyrazine (**4a**), indanone (**4b**), thiophene (**4d**), benzofuran (**4e**), and a caffeine derivative (**4g**). Other substrates required variation of the phosphine ligand for palladium to impart good reactivity. A survey of commercially available palladium pre-complexes was sufficient. Both a quinazolinone (**4c**) and a benzopyrazine

containing a free secondary amine (**4h**) were successfully cross-coupled using the PCy$_3$ Pd G4 pre-complex. Similarly, SPhos Pd G4 performed well in the cross-coupling with a bromo-benzothiazole (**4f**). Two examples, a benzocycloheptapyridine (**4k**, a derivatized form of Claritin®) and a pyridylfuranone (**4l**), demonstrated the amenability of this reaction to complex, highly functionalized, drug-like structures.

This organotrifluoroborate reagent, **6**, provided an opportunity to demonstrate the complementarity and orthogonality of these two distinct approaches (Scheme 4). As such, we executed a synthesis in which two trifluoromethyl alkenes were sequentially introduced and functionalized. Suzuki cross coupling of potassium trifluoromethylvinyl trifluoroborate **6** with brominated, masked trifluoromethyl alkene **1g** afforded α-trifluoromethyl styrene **5a** in good yield. Radical defluorinative alkylation of the trifluoromethyl alkene using diisopropylammonium bis(catecholato) (3-methoxypropyl) silicate provided *gem*-difluoroalkene **5b**, which subsequently underwent alcohol elimination to reveal an aliphatic trifluoromethyl alkene **5c** in good yield. Trifluoromethyl alkene **5c** then proceeded through a second selective radical defluorinative alkylation using N-Boc-pyrrolidine trifluoroborate to afford differentiated *gem*-difluoroalkene **5d**. Synthesis of such a structure by any other means would prove challenging, if not impossible, using state-of-the-art approaches.

Conclusions

In conclusion, two complementary approaches for the synthesis of highly functionalized trifluoromethyl alkenes have been realized. First, the viability of α-trifluoromethyl-β-silyl alcohols as masked trifluoromethyl alkenes was validated, enabling rapid diversification through several cross-coupling approaches. The elaborated products readily underwent elimination to generate their corresponding trifluoromethyl alkenes. Second, the one-step (trifluoromethyl)vinylation of functional group-rich aryl- and heteroaryl bromides was achieved using potassium tri-fluoromethylvinyl trifluoroborate. Taken together, these two complementary approaches provide the means to access an array of structurally diverse α-trifluoromethylated arenes rapidly that can be further leveraged to produce novel, fluorinated species.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

Table 4 Palladium cross-couplings with organotrifluoroborate[a]

a Unless otherwise noted, reactions were performed using bromide (1.0 equiv., 1 mmol), **6** (1.5 equiv.), Pd(OAc)$_2$ (5 mol%), PPh$_3$ (12 mol%), and Cs$_2$CO$_3$ (3 equiv.) in THF/H$_2$O (2 : 1, 0.11 M) at 80 °C for 18 h.
b Performed with PCy$_3$ Pd G4 in place of Pd source and ligand.
c Performed with SPhos Pd G4 in place of Pd source and ligand.
d Performed with XPhos Pd G4 in place of Pd source and ligand.
e Performed with Pd G4 dimer (2.5 mol%) in place of Pd source.
f Performed with Catacxium A Pd G3 in place of Pd source and ligand.

Notes and references

1 (a) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (c) K. W. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (d) K. Müeller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (e) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (f) C. F. Ni and J. B. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441.

2 (a) J. Xiao, B. Weisblum and P. J. Wipf, *J. Am. Chem. Soc.*, 2005, **127**, 5742; (b) E. Inokuchi, T. Marumi, A. Nilda, K. Kobayashi, K. Tomita, S. Oishi, H. Shno and N. Fujii, *J. Org. Chem.*, 2008, **73**, 3942; (c) K. Kobayahi, T. Marum, S. Oishi, H. Ohno and N. Fujii, *J. Org. Chem.*, 2009, **74**, 4626; (d) S. Fustero, G. Chiva, J. Piera, J. F. Sanz-Cervera, A. Volonterio, M. Zanda and C. Ramirez de Arellano, *J. Org. Chem.*, 2009, **74**, 3122.

3 R. Bakthavatchalam, Compounds useful for treating disorders related to trpa1, WO 2010138879, Dec 2, 2010.

4 (a) T. Woltering, W. Guba, H. Hilpert, A. Kuglstatter, A. Limberg, U. Obst Sander, E. Pinard and W. Wostl, Preparation of fluorooxazine derivatives for use as BACE1 inhibitors, WO 2014114532, July 31, 2014; (b) R. Bakthavatchalam, Compounds useful for treating disorders related to TRPA1, WO 2010138879, Dec. 2, 2010; (c) H. Mizuno, Preparation of pyridinyl oxadia-zolones for controlling pests, WO 2009066786, May 28, 2009; (d) M. G. Kelly, C. J. Kaub, J. Kincaid, S. Janagani, G. Wu, Z.-L. Wei, K. Sahasrabudhe, M. Duncton, R. B. Upasani, Y. Fang and M. Cox, Preparation of amide derivatives as ion-channel ligands, WO 2007100758, Sep 7, 2007; (e) M. G. Kelly, J. Kincaid, M. Duncton, K. Sahasrabudhe, S. Janagani, R. B. Upasani, G. Wu, Y. Fang and Z.-L. Wei, Preparation and biological activity of *N*-aryl and *N*-hetaryl substituted benzamides and pyridinecarboxamides as mammalian ion-channel ligands for using as anti-inflammatory and pain relief agents in pharmaceutical compositions, US 20060194801, Aug 31, 2006; (f) Y. Zhou, J. Qu, Y. Liu, and Y. Zhao, Preparation method and application of difluoroallyl borate, CN 106366105, Feb 1, 2017; (g) B. M. Trost and L. Debien, *J. Am. Chem. Soc.*, 2015, **137**, 11606.

5 (a) D. Barnes-Seeman, M. Jain, L. Bell, S. Ferreira, S. Cohen, X.-H. Chen, J. Amin, B. Snodgrass and P. Hatsis, *ACS Med. Chem. Lett.*, 2013, **4**, 514; (b) S. B. Lang, R. J. Wiles, C. B. Kelly and G. A. Molander, *Angew. Chem., Int. Ed.*, 2017, **56**, 15073; (c) T. Xiao, L. Li and L. Zhou, *J. Org. Chem.*, 2016, **81**, 7908; (d) L. Li, T. Xiao, H. Chem and L. Zhou, *Chem.– Eur. J.*, 2017, **23**, 2249; (e) K. Uneyama, Hydrogen Bonding in Organofluorine Compounds, in *Organofluorine Chemistry*, Blackwell Publishing, Oxford, UK, 2006.

6 Representative examples of this procedure: (a) B. M. Trost and L. Debien, *J. Am. Chem. Soc.*, 2015, **137**, 11606; (b) T. Kobayashi, T. Eda, O. Tamura and H. Ishibashi, *J. Org. Chem.*, 2002, **67**, 3156.

7 (a) R. Pana, X. Liua and M. Dengb, *J. Fluorine Chem.*, 1999, **2**, 167; (b) B. Jiang and Y. Xu, *J. Org. Chem.*, 1991, **56**, 7336; (c) O. Kobayashi, D. Uraguchi and T. Yamakawa, *J. Fluorine Chem.*, 2009, **130**, 591.

8 T. A. Hamlin, C. B. Kelly, R. M. Cywar and N. E. Leadbeater, *J. Org. Chem.*, 2014, **79**, 1145.

9 (a) D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780; (b) L. F. van Staden, D. Gravestock and D. Ager, *Chem. Soc. Rev.*, 2002, **31**, 194.

10 (a) J. C. Tellis, D. N. Primer and G. A. Molander, *Science*, 2014, **345**, 433; (b) M. Jouffroy, D. N. Primer and G. A. Molander, *J. Am. Chem. Soc.*, 2016, **138**, 475; (c) J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel and G. A. Molander, *Acc. Chem. Res.*, 2016, **49**, 1429; (d) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, *Nat. Rev. Chem.*, 2017, **1**(0052), 1.

11 (a) G. A. Molander, *J. Org. Chem.*, 2015, **80**, 7837; (b) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.

12 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564.

13 K. Kubota, J. Iwamoto and H. Ito, *Org. Biomol. Chem.*, 2017, **15**, 285.

14 (a) G. A. Molander and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 4302; (b) G. A. Molander, B. Canturk and L. E. Kennedy, *J. Org. Chem.*, 2009, **74**, 973.

15 (a) G. A. Molander and P. E. Gormisky, *J. Org. Chem.*, 2008, **73**, 7481; (b) J. R. Schmink, A. Bellomo and S. Berritt, *Aldrichimica Acta*, 2013, **46**, 71.

16 R. T. Thornbury and F. D. Toste, *Angew. Chem., Int. Ed.*, 2016, **55**, 11629.

17 Y. Liu, Y. Zhou, Y. Zhao and J. Qu, *Org. Lett.*, 2017, **19**, 946.

18 (a) T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508; (b) W. Tang, S. Keshipeddy, Y. Zhang, X. Wei, J. Savoie, N. D. Patel, N. K. Yee and C. H. Senanayake, *Org. Lett.*, 2011, **13**, 1366.

19 G. A. Molander, S. L. J. Trice and S. M. Kennedy, *J. Org. Chem.*, 2012, **77**, 8678.

20 Peterson Olefination, in *Comprehensive Organic Name Reactions and Reagents*, ed. Leo A. Paquette, 2010, vol. 491, p. 2176.

21 (a) J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science, Sausalito, CA, 2010; (b) A. Rudolph and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 2656.

22 D. N. Primer, I. Karakaya, J. C. Tellis and G. A. Molander, *J. Am. Chem. Soc.*, 2015, **137**, 2195.

23 D. J. Ager, The Peterson Olefination Reaction, *Org. React.*, 2004, **38**(1), 1–223.

24 (a) M. Jouffroy, D. N. Primer and G. A. Molander, *J. Am. Chem. Soc.*, 2016, **138**, 475; (b) K. Lin, C. B. Kelly, M. Jouffroy and G. A. Molander, *Org. Synth.*, 2017, **94**, 1625.

25 M. Jouffroy, C. B. Kelly and G. A. Molander, *Org. Lett.*, 2016, **18**, 876.