Radical Reactions

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Oxidation of Alkyl Trifluoroborates: An Opportunity for Tin-Free Radical Chemistry**

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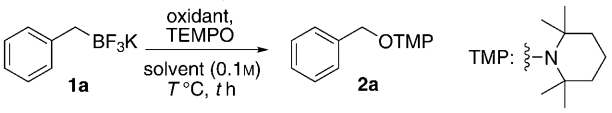
As a result of its unique attributes, radical chemistry offers intriguing synthetic opportunities which are now fully recognized and belong to mainstream chemistry.[1] Nowadays the challenge is to develop more scalable and ecocompatible reactions and to notably circumvent the use of tin reagents, which has remained so far the traditional option.[2,3] In that context, redox processes[4] have held great promise as recently illustrated by several research groups through asymmetric transformations and their applications to the synthesis of natural products.[5]

While oxidation of classical organometallic compounds such as Grignard or lithium reagents is well-known, this approach suffers from the drawbacks associated with organometallic chemistry—stringent reaction conditions and poor tolerance of a variety of function groups.[6] Inspired by the seminal work of Kumada and co-workers on organopentafluorosilicate compounds,[7] we reasoned that the oxidation of softer organometallic derivatives was possible and we focused our attention on the now well-developed organotrifluoroborate compounds as precursors to radical species.[8] Moreover, their oxidation chemistry has remained largely unexplored.[9,10]

To initially probe our design, we examined the behavior of benzyl trifluoroborate **1a**, bearing in mind that the benzyl radical should be an easy one to generate and that trapping with TEMPO[11] would give strong evidence for the radical intermediate formation (adduct **2a**; Table 1). A preliminary screening of the reaction conditions provided valuable information. We initially ran reactions with $Cu(OAc)_2$ as the oxidant and a default of 0.5 equivalents of TEMPO to easily monitor the reactions by TLC. While the reaction did not proceed in hydrocarbon solvents and was rather sluggish in alcohols (34% of **2a** in *t*BuOH; Table 1, entry 1), the use of DMSO provided better results (Table 1, entry 2). Remarkably, a good yield of **2a** was also observed in a H_2O/DMSO (9:1) mixture (Table 1, entry 3). In DMSO, copper salts proved to be superior to ferrocenium salts or CAN. Interestingly, $CuCl_2$ was successful in Et_2O at room temperature (Table 1, entry 8).[12]

Table 1: Oxidation of benzyl substrate **1a**.



1a **2a**

Entry	Oxidant (1.2 equiv)	Reaction conditions[a]	**2a**, yield [%]
1	$Cu(OAc)_2$	*t*BuOH, 80°C, 20 h	34
2	$Cu(OAc)_2$	DMSO, 120°C, 6 h	88
3	$Cu(OAc)_2$	H_2O/DMSO (9:1), 100°C, 14 h	72
4	$Cu(OAc)_2$	DMSO, 120°C, 4.5 h	85
5	$Cu(EH)_2$	DMSO, 120°C, 3.5 h	73
6	$FeCp_2BF_4$	DMSO, 120°C, 5 h	28
7	$CuCl_2$	DMSO, 120°C, 3.5 h	66
8	$CuCl_2$	Et_2O,[b] RT, 14 h	72
9	CAN	DMSO, 50°C, 24 h	49

[a] Entries 1–3: 0.5 equivalents of TEMPO; entries 4–6: 1.2 equivalents of TEMPO; entries 7–9: 3 equivalents of TEMPO. [b] Concentration of 0.2 M. CAN = ceric ammonium nitrate, Cp = cyclopentadienyl, $Cu(EH)_2$ = copper 2-ethylhexanoate, DMSO = dimethyl sulfoxide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical.

Having defined an appropriate set of reaction conditions, we then studied the reactivity of other substrates (Table 2). As expected, allyl substrate **1b** provided good yields of TEMPO adduct **2b** in conditions similar to the oxidation of **1a** (Table 2, entries 1 and 2). We then looked at the alkyl series. Hexenyl substrate **1c** was oxidized under the same type of conditions and gave, as the major product, linear adduct **2c*L*** accompanied by about 10% of cyclized product **2c*C***. Substrate **1c** was also oxidized by Dess–Martin periodinane[13] in Et_2O at room temperature and delivered only **2c*L***. These findings are consistent with a very rapid TEMPO trapping of the hexenyl radical intermediate, which has little time to cyclize,[14] especially at room temperature because of a lower cyclization rate constant.[15] Secondary and tertiary substrates proved to be easy to oxidize under mild conditions using $CuCl_2$ at room temperature or DMP (Table 2, entries 5–10). Gratifyingly, other functionalized organotrifluoroborate compounds[16] **1h–j** were amenable to this oxidation process, as illustrated in Scheme 1 by the formation of TEMPO adducts such as **2h** bearing a benzyl ether group, the fragile ketone **2i**,[17] and the very intriguing allylsilane **2j**. Thus, this process is compatible with function groups that are susceptible to nucleophilic attack and oxidation.

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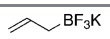
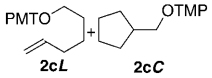
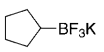
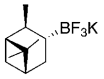
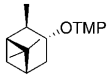
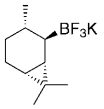
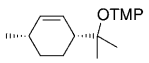
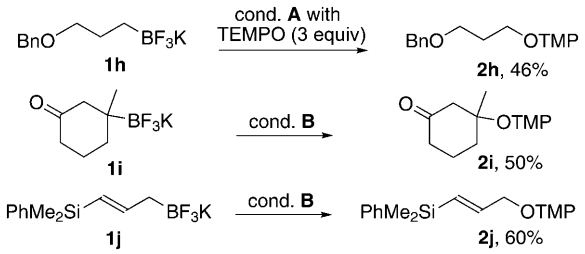
Table 2: Oxidation of trifluoroborates **1**.

Entry	Substrate	Oxidant, conditions[a]	Product, yield [%]
			
1	**1b**	$Cu(EH)_2$, **A**	**2b**, 75
2	**1b**	$Cu(OAc)_2$, **A**	**2b**, 72
			
3	**1c**	$Cu(EH)_2$, **A**	**2cL**/**2cC** (89:11), 57
4	**1c**	DMP, **B**	**2cL**/**2cC** (100:0), 50
			
5	**1d**	$CuCl_2$, **B**	**2d**, 63
6	**1d**	DMP, **B**	**2d**, 64
			
7	**1e**	$CuCl_2$, **B**	**2e**, 64
8	**1e**	DMP, **B**	**2e**, 82
			
9	**1f**	$CuCl_2$, **B**	**2f**, quant.
10	**1f**	DMP, **B**	**2f**, 85
			
11	**1g**	$CuCl_2$, **B**	**2g**, 67

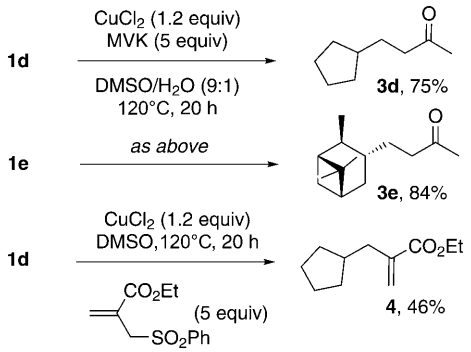
[a] Conditions **A**: 1.2 equivalents of TEMPO, DMSO (0.1 M), 120 °C, 20 h; conditions **B**: 3 equivalents of TEMPO, Et_2O (0.2 M), RT, 24–48 h. DMP = Dess–Martin periodinane.



Scheme 1. Fuctionalized organotrifluoroborate compounds. Bn = benzyl.

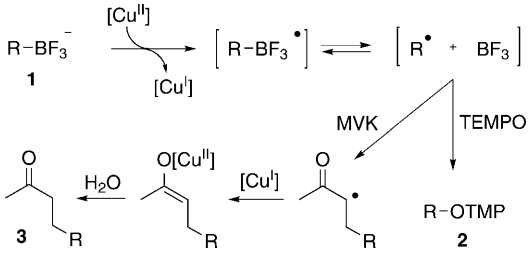
We then sought further confirmation on the radical character of these transformations. A primary indication came from the observed formation of cyclopentyl product **2cC**, which presumably originates from a 5-*exo*-trig radical cyclization process. Running the reaction in a more dilute medium (0.01 M in DMSO at 120 °C, 72 h) resulted in an increased formation of **2cC** (**2cL**/**2cC** (73:27), 29% yield), thus suggesting a closer competition between the TEMPO trapping and the 5-*exo*-trig cyclization. Along the same lines, the stereoselectivity in the formation of **2e** is consistent with the intervention of a radical intermediate[18] as is the ring opening of **1g** to give cylohexene **2g**. We also examined the possibility of applying this method for C–C bond formation. Thus, heating a 0.5 M solution of **1a** in the presence of $Cu(OAc)_2$ at 120 °C provided 70% of 1,2-diphenylethane, which resulted from the dimerization of the benzyl radical, accompanied by oxidation by-products (benzyl alcohol, benzaldehyde).

However, more meaningful from a synthetic point of view is the possibility of operating Giese-type reactions with the addition of MVK on secondary trifluoroborates to produce ketones **3d** or **3e** (Scheme 2). In the latter case, only one diastereomer was isolated.[19] Furthermore, allylation to give acrylate **4** was also achieved.



Scheme 2. Formation of C–C bonds. MVK = methyl vinyl ketone.

Although a plausible mechanism is still speculative, we think that a single-electron transfer from the oxidant generates a transient radical species R• that can be trapped by TEMPO to generate adducts **2** or trapped by MVK to produce ketones **3** (Scheme 3). In the latter case, we found the role of water to be highly beneficial to guarantee good yields. A possible rationalization would be an in situ well-controlled hydrolysis of the copper enolate species.[7]



Scheme 3. Mechanism proposal.

In conclusion, we have shown that it is possible to oxidize allyl and alkyl trifluoroborates with copper(II) salts and DMP. Appropriate reaction conditions have been developed for each class of substrates (primary to tertiary). This new method of radical generation is compatible with functionalization and C–C bond formation and augurs well for further elaborations, and these results will be report in due course.

Experimental Section

Preparation of 4-isopinocamphenyl-2-butanone (**3e**): A mixture of potassium trifluoroborate salt **1e** (244 mg, 1 mmol), $CuCl_2$ (161 mg, 1.2 mmol, 1.2 equiv), and methyl vinyl ketone (0.4 mL, 5 mmol, 5 equiv) in DMSO/water (9:1; 5 mL) was heated at 120 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with water (20 mL), and extracted with Et_2O (2 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **3e** as a colorless oil (176 mg, 84 %). IR (neat): $\nu = 2918, 2359, 2341, 1716, 1366\ cm^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.70$ (d, $J = 9.7$ Hz, 1H, H7), 0.96 (s, 3H, H11 or H12), 0.99 (d, $J = 7.0$ Hz, 3H, H13), 1.16 (s, 3H, H12 or H11), 1.34–1.45 (m, 2H, H3 and H9), 1.50–1.68 (m, 2H, H4 and H5), 1.70–1.85 (m, 2H, H3′ and H6), 1.85–1.91 (m, 1H, H8), 2.06–2.15 (m, 1H, H9′), 2.13 (s, 3H, H13), 2.22–2.30 (m, 1H, H7′), 2.34 (ddd, 1H, $J = 16.5$, 10.4, 5.1 Hz, H2), 2.46 ppm (ddd, 1H, $J = 16.5$, 10.1, 5.9 Hz, 1H, H2′); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 21.7$ (C13), 23.0 (C11 or C12), 28.1 (C11 or C12), 30.0 (C14), 34.1 (C7), 34.5 (C9), 34.8 (C3), 36.1 (C4), 38.8 (C10), 42.0 (C8), 42.3 (C2), 43.7 (C5), 48.2 (C6), 209.5 ppm (C1). HRMS calcd for $C_{14}H_{25}O$ ($[M+H]^+$): 209.1899, found: 209.1900.

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[1] a) *Radicals in Organic Synthesis* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**; b) *Radicals in Synthesis I & II*, *Vols. 263 & 264* (Ed.: A. Gansäuer), Springer, Berlin, **2006**; c) G. J. Rowlands, *Tetrahedron* **2009**, *65*, 8603 – 8655; d) G. J. Rowlands, *Tetrahedron* **2010**, *66*, 1593 – 1636.

[2] a) P. A. Baguley, J. C. Walton, *Angew. Chem.* **1998**, *110*, 3272 – 3283; *Angew. Chem. Int. Ed.* **1998**, *37*, 3072 – 3082; b) A. Studer, S. Amrein, *Synthesis* **2002**, 835 – 849; c) B. C. Gilbert, A. F. Parsons, *J. Chem. Soc. Perkin Trans. 2* **2002**, 367 – 397.

[3] For very recent contributions, see: a) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe, C. R. J. Stephenson, *Org. Lett.* **2010**, *12*, 368 – 371; b) T. Taniguchi, N. Goto, A. Nishibata, H. Ishibashi, *Org. Lett.* **2010**, *12*, 112 – 115; c) S.-H. Ueng, A. Solovyev, X. Yuan, S. J. Geib, L. Fensterbank, E. Lacôte, M. Malacria, M. Newcomb, J. C. Walton, D. P. Curran, *J. Am. Chem. Soc.* **2009**, *131*, 11256 – 11262, and references therein.

[4] For a review, see: P. I. Dalko, *Tetrahedron* **1995**, *51*, 7579 – 7653.

[5] For recent contributions, see: a) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124 – 4125; b) M. Amatore, T. D. Beeson, S. P. Brown, D. W. C. McMillan, *Angew. Chem.* **2009**, *121*, 5223 – 5226; *Angew. Chem. Int. Ed.* **2009**, *48*, 5121 – 5124; c) M. P. DeMartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546 – 11560; d) U. Jahn, E. Dinca, *Chem. Eur. J.* **2009**, *15*, 58 – 62; e) K. C. Nicolaou, R. Reingruber, D. Sarlah, S. Bräse, *J. Am. Chem. Soc.* **2009**, *131*, 2086 – 2087; see also: f) M. A. Ischay, M. E. Anzovino, J. Du, T. Yoon, *J. Am. Chem. Soc* **2008**, *130*, 12886 – 12887; g) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756 – 8757; h) A. Wetzel, G. Pratsch, R. Kolb, M. R. Heinrich, *Chem. Eur. J.* **2010**, *16*, 2547 – 2556.

[6] For TEMPO-mediated oxidations, see: a) M. S. Maji, T. Pfeifer, A. Studer, *Angew. Chem.* **2008**, *120*, 9690 – 9692; *Angew. Chem. Int. Ed.* **2008**, *47*, 9547 – 9550; b) T. Nagashima, D. P. Curran, *Synlett* **1996**, 330 – 332; c) see also: M. Pouliot, P. Renaud, K. Schenk, A. Studer, T. Vogler, *Angew. Chem.* **2009**, *121*, 6153 – 6156; *Angew. Chem. Int. Ed.* **2009**, *48*, 6037 – 6040, and references therein.

[7] K. Tamao, J.-I. Yoshida, H. Yamamoto, T. Kakui, H. Matsumoto, M. Takahashi, A. Kurita, M. Murata, M. Kumada, *Organometallics* **1982**, *1*, 355 – 368.

[8] a) H. A. Stefani, R. Cella, A. S. Vieira, *Tetrahedron* **2007**, *63*, 3623 – 3658; b) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275 – 286; c) S. Darses, J.-P. Genêt, *Chem. Rev.* **2008**, *108*, 288 – 325.

[9] Cu^{II} oxidation of boranes in halogenation reactions is known, see: a) C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415 – 3434, and references therein, notably: b) C. F. Lane, *J. Organomet. Chem.* **1971**, *31*, 421 – 431.

[10] Electrochemical oxidation of polyphenyltrifluoroborate anions is known, see: a) L. A. Shundrin, V. V. Bardin, H.-J. Z. Frohn, *Z. Anorg. Allg. Chem.* **2004**, *630*, 1253 – 1257; for PET oxidation of allyl- and benzyltrifluoroborates, see: b) Y. Nishigaichi, T. Orimi, A. Takuwa, *J. Organomet. Chem.* **2009**, *694*, 3837 – 3839; see also for other borates: c) G. B. Schuster, *Pure Appl. Chem.* **1990**, *62*, 1565 – 1572; for the oxidation of arylboronic acids with $Mn(OAc)_3$, see: d) A. Dickschat, A. Studer, *Org. Lett.* **2010**, *12*, 3972 – 3974, and references therein; see also: e) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 13194 – 13196; for a Ritter reaction of trifluoroborates involving a two-electron oxidation, see: f) C. Carzola, E. Métay, B. Andrioletti, M. Lemaire, *Tetrahedron Lett.* **2009**, *50*, 6855 – 6857.

[11] For a review on the use of TEMPO, see: T. Vogler, A. Studer, *Synthesis* **2008**, 1979 – 1993.

[12] Under these conditions, an excess amount of TEMPO (3 equiv) was used. TEMPO and $CuCl_2$ are known to form a complex, see: J. Laugier, J.-M. Latour, A. Caneschi, P. Rey, *Inorg. Chem.* **1991**, *30*, 4474 – 4477.

[13] For the oxidation of hydroxy-substituted trifluoroorganoborates with hypervalent iodine derivatives, see: G. A. Molander, D. E. Petrillo, *J. Am. Chem. Soc.* **2006**, *128*, 9634 – 9635.

[14] a) See Ref. [6b]; b) V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc.* **1992**, *114*, 4992 – 4996; solvents effects may also be at play: c) A. L. J. Beckwith, V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc.* **1992**, *114*, 4983 – 4992.

[15] C. Chatgilialoglu, K. U. Ingold, J. C. Scaiano, *J. Am. Chem. Soc.* **1981**, *103*, 7739 – 7742.

[16] For examples of functionalized organotrifluoroborates, see: a) G. A. Molander, J. Ham, *Org. Lett.* **2006**, *8*, 2031 – 2034; b) G. A. Molander, W. Febo-Ayala, M. Ortega-Guerra, *J. Org. Chem.* **2008**, *73*, 6000 – 6002.

[17] Adduct **2i** undergoes rapid elimination to furnish the corresponding cyclohexenone.

[18] a) C. Ollivier, R. Chuard, P. Renaud, *Synlett* **1999**, 807 – 809; b) C. Cadot, P. I. Dalko, J. Cossy, C. Ollivier, R. Chuard, P. Renaud, *J. Org. Chem.* **2002**, *67*, 7193 – 7202.

[19] The stereochemistry of **3e** is assigned by analogy with product **2e**.

