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Exploration of mild copper-mediated coupling of organotrifluoroborates in the synthesis of thiirane-based inhibitors of matrix metalloproteinases

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ABSTRACT

The copper-mediated and non-basic oxidative cross-coupling of organotrifluoroborates with phenols was applied to elaboration of the structures of thiirane-based inhibitors of matrix metalloproteinases. By revision of the synthetic sequence to allow this cross-coupling as the final step, and taking advantage of the neutral nature of organotrifluoroborate cross-coupling, a focussed series of inhibitors showing aryloxy and alkenyloxy replacement of the phenoxy substituent was prepared. This reaction shows exceptional promise as an alternative to the classic copper-mediated but strongly basic Ullmann reaction, for the diversification of ether segments within base-labile lead structures.

There is a high demand for new synthetic methods for the preparation of diaryl ethers and alkenyl aryl ethers, owing to their importance as structural motifs in a wide range of molecules with various applications. The classical reaction for preparation of diaryl ethers is the copper-catalyzed Ullmann reaction, but this reaction is typically carried out at high temperatures in the presence of strong base, which significantly limits its use.[1] Recently, Batey and Quach have reported a novel protocol for ether formation from alcohols under essentially neutral conditions, using alkenyl and aryl trifluoroborate salts in the presence of copper.[2] This method is of interest because of its mildness, which allows application to valuable and highly elaborated synthetics substrates.

In recent years, potassium organotrifluoroborates have become a promising alternative to the use of organoboronic acids. Organotrifluoroborates are crystalline solids that show exceptional stability toward oxygen and moisture, and they are easily prepared.[3] Many are now commercially available. Moreover, in many organic reactions potassium organotrifluoroborates have shown comparable and very often better yields compared to organoboronic acids. In addition, the tetracoordinated nature of these species allows their functionalization, increasing the molecular complexity of the organoboron reagent, providing a unique access to valuable organic synthons.[4]

We have previously described the synthesis, inhibitory activity,[5,6] mechanism[7,8] and metabolism studies[9,10] with a valuable class of thiirane-containing highly selective gelatinase inhibitors, of which **1** (also known as SB-3CT; Fig. 1) is a prototype. This inhibitor potently inhibits gelatinases (MMP-2 and MMP-9) in the nanomolar range, to the virtual exclusion of the other members of the MMP family. Compound **1** is a mechanism-based inhibitor, which operates by a distinct mechanism that gives rise to a stable complex with the gelatinases involving thiolate coordination to the active-site zinc atom. An important feature of the inhibitor is the biphenyl ether moiety that fits into the S1′ pocket of these gelatinases, and a thiirane ring that undergoes a gelatinase-catalyzed ring opening to give the stable zinc–thiol interaction of the inhibited enzyme.[11]

Despite its rapid metabolism in mice and other species,[10] compound **1** is highly effective in animal models of several diseases.[12–20] This efficacy is in large measure due to the high gelatinase activity of one of its major metabolites.[10] Although more potently active than compound **1**, it has certain undesirable properties such as poor aqueous solubility, difficulty in formulation, and multiple routes of metabolism that all present obstacles to the progression of this compound in pharmacological evaluation.

SAR studies of variants of compound **1** carried out in our lab to date have shown that the structural template can be modified to

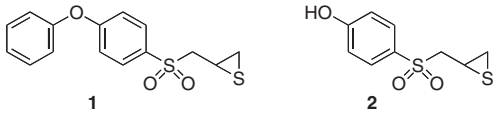

Figure 1. SB-3CT (**1**), a potent and selective gelatinase inhibitor and intermediate base-labile phenol **2**.

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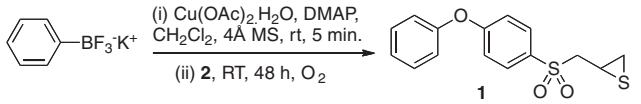
Table 1
Optimization experiment for Cu(II)-mediated etherification of the base-labile phenol **2** to produce compound **1**



Entry	Equiv $Cu(OAc)_2$	Equiv DMAP	Temperature	Yield[a] (%)
1	0.1	0.2	rt	26 (61)
2	0.1	2	rt	0 (14)
3	1	0.2	reflux	24 (29)
4	1	0.2	rt	72(0)

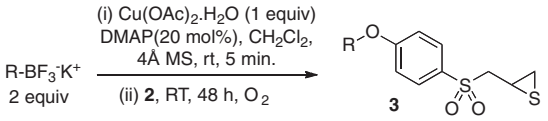
[a] Isolated yield; data in parentheses are the recovered starting materials.

improve solubility and metabolic stability of the compound class, concomitant with retention of selectivity and potency in inhibition of gelatinases. Furthermore, in some cases, it was possible to tweak the chemical structure to inhibit only MMP-2. Yet, in others the modifications gave rise to a widening of the spectrum of inhibited MMPs. These results reveal the richness of the structural space for the thiirane inhibitors, which is worthy of further exploration in generating libraries of structurally diverse molecules.

In order to aggressively develop this SAR, we have focused on the syntheses of structurally diverse libraries for biological evaluation. Here, we report our efforts toward the diversification of the phenoxy segment of **1**. This ambition required a synthetic route wherein the diversification occurs at the final step of the synthesis, from a common intermediate, under conditions that are compatible with the other functionalities present in the molecule.

We have prepared compound **2** in five synthetic steps from 4-hydroxythiophenol in the context of a focused series of sulfonate derivatives of the thiirane inhibitors.[21] The thiirane ring of **2** is readily opened by base, by a mechanism identical to that which occurs in matrix metalloproteinase inhibition. Consequently, **2** is incompatible as a reagent for traditional Ullmann ether formation. Indeed, in our hands even the milder Ullmann conditions given by Chan and Evans[22,23] (2 equiv boronic acid, 1 equiv $Cu(OAc)_2$, 2 equiv Et_3N, molecular sieves, rt) were unsuccessful.

Table 2
The Cu(II)-mediated etherification of phenol **2** with different $RBF_3^-K^+$ salts



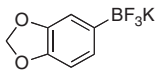
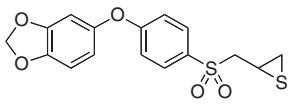
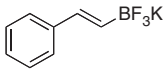
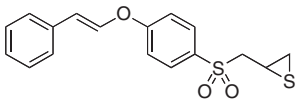
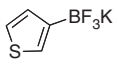
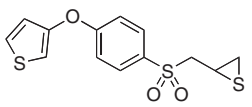
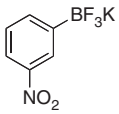
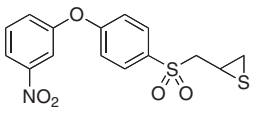
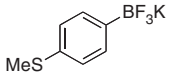
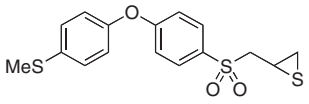
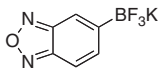
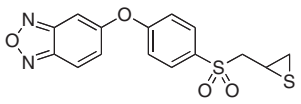
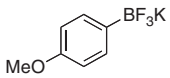
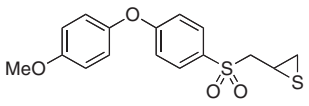
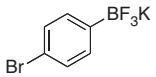
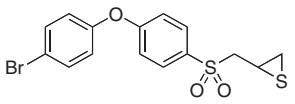
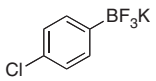
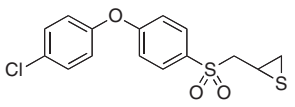
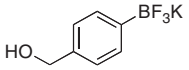
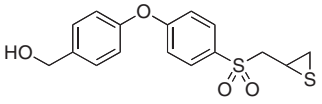
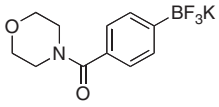
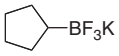
Entry	Trifluoroborate	Product	Yield[a] (%)
1			44 (33)
2			65 (0)
3			36 (0)
4			39 (0)
5			74 (0)
6			16 (27)
7			53(15)
8			14(57)
9			24(33)

Table 2 (*continued*)

Entry	Trifluoroborate	Product	Yield[a] (%)
10			14(41)
11		–	0 (12)
12		–	0 (78)

[a] Isolated yield; data in parentheses are the recovered starting materials.

As a final effort to enable Ullmann cross-coupling diversification from **2** as an intermediate, we explored the use of aryl trifluoroborates for phenol *O*-arylation as described by Batey and Quach. The result from the initial reaction (Table 1, entry 1). was encouraging. Given the modest yield for **1**, and the intrinsic complexity of this reaction—key variables include the choice of copper salt catalyst, catalyst loading, catalyst ligand, reagent stoichiometry, solvent, temperature, oxidant, and nature of the molecular sieves and its source—we explored many of these variables as a prelude to library diversification. $Cu(OAc)_2$ was chosen as the Cu(II) source. The addition of 1,2-dimethylimidazole[24] and *N*-methylimidazole[25] monodentate copper ligands, as were recently used in similar copper-catalyzed cross-couplings, gave a small increase in the reaction yield. 1,2-Dimethylimidazole was the better ligand of the two. DMSO and MeCN as sole solvents, or as co-solvents (in different ratios) with dichloromethane, were compared to dichloromethane alone. None of these changes improved the yields. The use of 5 equiv (instead of 2 equiv) of the potassium phenyltrifluorborate actually reduced the yield. This outcome may be attributed to phenyltrifluorborate homocoupling.[24] Furthermore, we discovered that different sources for the molecular sieves, all exhaustively activated at 200 °C under vacuum prior to use, gave different yields. These differences may be attributed to the variability of the constituents and the mixtures of ingredient minerals in different molecular sieves from different origins.

As is shown in Table 1, we decided to increase the amount of copper using DMAP as ligand. We found that 1 equiv of $Cu(OAc)_2$, 0.2 equiv of DMAP, 2 equiv of potassium phenyltrifluoroborate in the presence of 4 Å molecular sieves gave the best results for this funtionalization (Table 1, entry 4). As Batey and Quach observed previously, under these conditions, phenylboronic acid also undergoes cross-coupling with phenol **2**, although in lower yield (with 15% of cross-coupling product and 49% of starting material recovered).

We realize that when the number of components for the reaction is many (as is required for this reaction), many different conditions could be tried. Regardless, the conditions given in Table 1, entry 4, were satisfactory and we were poised to prepare a series of analogs of compound **1** by this method. The results of these efforts are given in Table 2.

As Batey and Quach noted, electron-rich aryl trifluoroborates give the best results (Table 2, entries 5 and 7), whereas electron-deficient aryl trifluoroborates with electron-withdrawing groups at the *para* position and alkyl organotrifluoroborates did not react, when treated with phenol **2** (Table 2, entries 11 and 12). However, the electron-deficient potassium 3-nitrophenyltrifluoroborate (Table 2, entry 4), with an electron-withdrawing group at the *meta* position, furnished the desired product in a moderate yield. With the exception of potassium *trans*-styryltrifluoroborate (Table 2, entry 2), alkenyl and heterocyclic trifluoroborates were modest cross-coupling partners (Table 2, entries 3 and 6).

The mechanism of this copper-mediated oxidative coupling with organotrifluoroborates is believed to go through a Cu^{III} species. Stahl and co-workers[26] have suggested that after the initial transmetallation, the resulting aryl-Cu^{II} species is oxidized by another equivalent of Cu^{II} to yield an aryl-Cu^{III} intermediate, which undergoes facile C–O reductive elimination.

Notwithstanding the modesty in yields, the procedure employed in the present study allows for a single-step rapid assembly of a series of analogs of **1** with variations in the ether moiety in the last step on a structurally sensitive precursor. We have expanded the mild and essentially neutral conditions developed by Batey and Quach for the syntheses of alkenyl–aryl and aryl–aryl ethers. The reaction was successfully applied to the base-labile thiirane **2** to generate a series of analogs of gelatinase inhibitor **1**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.12.076.

References and notes

1. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
2. Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381.
3. (a) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49; (b) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623; (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275; (d) Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288.
4. Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2008**, *73*, 3885. and references therein.
5. Brown, S.; Bernardo, M. M.; Li, Z. H.; Kotra, L. P.; Tanaka, Y.; Fridman, R.; Mobashery, S. *J. Am. Chem. Soc.* **2000**, *122*, 6799.
6. Lee, M.; Bernardo, M. M.; Meroueh, S. O.; Brown, S.; Fridman, R.; Mobashery, S. *Org. Lett.* **2005**, *7*, 4463.
7. Forbes, C.; Shi, Q.; Fisher, J. F.; Lee, M.; Hesek, D.; Llarrull, L. I.; Toth, M.; Gossing, M.; Fridman, R.; Mobashery, S. *Chem. Biol. Drug Des.* **2009**, *74*, 527.
8. Tao, P.; Fisher, J. F.; Mobashery, S.; Schlegel, H. B. *Org. Lett.* **2009**, *11*, 2559.
9. Celenza, G.; Villegas-Estrada, A.; Lee, M.; Boggess, B.; Forbes, C.; Wolter, W. R.; Suckow, M. A.; Mobashery, S.; Chang, M. *Chem. Biol. Drug Des.* **2008**, *71*, 187.
10. Lee, M.; Villegas-Estrada, A.; Celenza, G.; Boggess, B.; Toth, M.; Kreitinger, G.; Forbes, C.; Fridman, R.; Mobashery, S.; Chang, M. *Chem. Biol. Drug Des.* **2007**, *70*, 371.
11. Ikejiri, M.; Bernardo, M. M.; Bonfil, R. D.; Toth, M.; Chang, M.; Fridman, R.; Mobashery, S. *J. Biol. Chem.* **2005**, *280*, 33992.
12. Bonfil, R. D.; Sabbota, A.; Nabha, S.; Bernardo, M. M.; Dong, Z.; Meng, H.; Yamamoto, H.; Chinni, S. R.; Lim, I. T.; Chang, M.; Filetti, L. C.; Mobashery, S.; Cher, M. L.; Fridman, R. *Int. J. Cancer* **2006**, *118*, 2721.
13. Kruger, A.; Arlt, M. J. E.; Gerg, M.; Kopitz, C.; Bernardo, M. M.; Chang, M.; Mobashery, S.; Fridman, R. *Cancer Res.* **2005**, *65*, 3523.
14. Martin, M. D.; Carter, K. J.; Jean-Philippe, S. R.; Chang, M.; Mobashery, S.; Thiolloy, S.; Lynch, C. C.; Matrisian, L. M.; Fingleton, B. *Cancer Res.* **2008**, *68*, 6251.

15. Gu, Z.; Cui, J.; Borwn, S.; Fridman, R.; Mobashery, S.; Strongin, A. Y.; Lipton, S. A. *J. Neurosci.* **2005**, *25*, 6401.
16. Ota, R.; Kurihara, C.; Tsou, T. L.; Young, W. L.; Yeghiazarians, Y.; Chang, M.; Mobashery, S.; Sakamoto, A.; Hashimoto, T. *J. Cereb. Blood Flow Metab.* **2009**, *29*, 1547.
17. Luplertlop, N.; Misse, D.; Bray, D.; Deleuze, V.; Gonzalez, J. P.; Leardkamolkarn, V.; Yssel, H.; Veas, F. *EMBO Rep.* **2006**, *7*, 1176.
18. Guo, Z.; Sun, X.; He, Z.; Jiang, Y.; Zhang, X.; Zhang, J. H. *Neurol. Res.* **2010**, *32*, 715.
19. He, Z. J.; Huang, Z. T.; Chen, X. T.; Zou, Z. *J. Chin. Med. (Engl.)* **2009**, *122*, 2346.
20. Yu, F.; Kamada, H.; Niizuma, K.; Endo, H.; Chan, P. H. *J. Neurotrauma* **2008**, *25*, 184.
21. Testero, S. A.; Lee, M.; Staran, R. T.; Espahbodi, M.; Llarrull, L. I.; Toth, M.; Mobashery, S.; Chang, M. *ACS Med. Chem. Lett*. doi:10.1021/ml100254e [Epub ahead of print].
22. Chan, D. M. T.; Monaco, K. L.; Wang, R. P. *Tetrahedron Lett.* **1998**, *39*, 2933.
23. Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.
24. Jouvin, K.; Couty, F.; Evano, G. *Org. Lett.* **2010**, *12*, 3272.
25. Bolshan, Y.; Batey, R. A. *Tetrahedron* **2010**, *66*, 5283.
26. King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044.