

Tri- and Tetrasubstituted Functionalized
Vinyl Sulfides by Radical Allylation

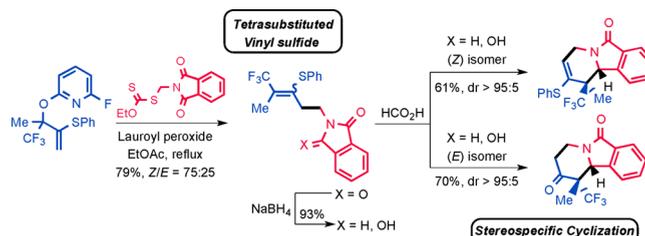
Laurent Debien, Marie-Gabrielle Braun, Béatrice Quiclet-Sire, and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652 Ecole Polytechnique,
91128 Palaiseau Cedex, France

Zard@poly.polytechnique.fr

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ABSTRACT



2-Fluoropyridinyl-6-oxy-precursors derived from phenyl vinyl sulfide react with radicals generated from xanthates *via* an addition–elimination process to furnish the corresponding vinyl sulfides in good yields. This convergent method is operationally simple and enables a straightforward synthesis of the difficult to access tetrasubstituted vinyl sulfides. Vinyl sulfides were used as more robust enol ether surrogates in highly stereoselective reactions with *N*-acylium cations leading to nitrogen-containing polycyclic structures.

Vinyl sulfides are versatile building blocks that have been widely used as more robust surrogates for enol ethers¹

(1) See, for example: (a) Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250. (b) Sasmal, P. K.; Maier, M. E. *Org. Lett.* **2002**, *4*, 1271. (c) Sasmal, P. K.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 824. For applications in total synthesis, see: (d) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. (e) Paquette, L. A.; Sun, L.-Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Org. Chem.* **1997**, *62*, 8155.

(2) For synthetic applications, see: (a) Schneebeli, S.; Kamenestka, M.; Foss, F.; Vazquez, H.; Skouta, R.; Hybertsen, M.; Venkataraman, L.; Breslow, R. *Org. Lett.* **2010**, *12*, 4114. (b) Cui, Y.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 1720. (c) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.

(3) For selected examples, see: (a) Pearson, W. H.; Lee, I. Y.; Mi, Y.; Stoy, P. *J. Org. Chem.* **2004**, *69*, 9109. (b) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (c) Shaikh, A. K.; Cobb, A. J. A.; Varvounis, G. *Org. Lett.* **2012**, *14*, 584. (d) Dittami, J. P.; Nie, X. Y.; Nie, H.; Ramanathan, H.; Buntel, T.; Rigatti, S. *J. Org. Chem.* **1992**, *57*, 1151.

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(6) For selected examples, see: (a) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed.* **2000**, *39*, 1664. (b) Szilágyi, A.; Fenyvesi, F.; Mayercsik, O.; Pelyvás, I. S.; Bácskay, I.; Fehér, P.; Váradi, J.; Vecsernyés, M.; Herczegh, P. *J. Med. Chem.* **2006**, *49*, 5626. (c) Sader, H. S.; Johnson, D. M.; Jones, R. N. *Antimicrob. Agents Chemother.* **2004**, *48*, 53.

in reactions involving thionium ions,² in cycloadditions,³ or in carbometalation processes.⁴ This structural motif has also found applications in material science⁵ and is featured in some biologically active compounds.⁶ Not unexpectedly, vinyl sulfides have attracted continuing interest from the synthetic community, and a variety of methods have been reported for their preparation. The main approaches include the free radical,⁷ base,⁸ or metal⁹ mediated hydrothiolation of alkynes, the cross-coupling¹⁰ of thiols with functionalized vinylic reagents, and the reaction of unsaturated compounds with electrophilic sulfur reagents.¹¹

(7) See, for example: (a) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L. *Chem. Lett.* **1987**, 1647. (b) Benati, L.; Capella, L.; Montevicchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1035. (c) Lo Conte, M.; Pacifico, S.; Chambery, A.; Marra, A.; Dondoni, A. *J. Org. Chem.* **2010**, *75*, 4644.

(8) For recent examples, see: (a) Waters, M. S.; Cowen, J. A.; McWilliams, J. C.; Maligres, P. E.; Askin, D. *Tetrahedron Lett.* **2000**, *41*, 141. (b) Yu, A. H.; Qiu, R. H.; Tan, N. Y.; Peng, L. F.; Xu, X. H. *Chin. Chem. Lett.* **2011**, *22*, 687. (c) Kondoh, A.; Takami, K.; Yorimitsu, H.; Oshima, K. *J. Org. Chem.* **2005**, *70*, 6468.

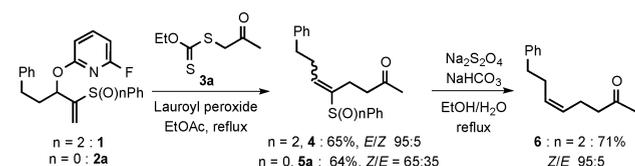
(9) Many metals can trigger this transformation; for a review, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. See, also: (b) Di Giuseppe, A.; Castarlenas, R.; Pérez-Torrente, J. J.; Crucianelli, M.; Polo, V.; Sancho, R.; Lahoz, F. J.; Oro, L. A. *J. Am. Chem. Soc.* **2012**, *134*, 8171.

(10) For a recent review, see: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. See, also: (b) Lin, Y.-Y.; Wang, Y.-J.; Lin, C.-H.; Cheng, J.-H.; Lee, C.-F. *J. Org. Chem.* **2012**, *77*, 6100. (c) Kao, H. L.; Lee, C. F. *Org. Lett.* **2011**, *13*, 5204.

Paradoxically, despite the plethora of transformations available,¹² only a handful of methods allow for the construction of tetrasubstituted vinyl sulfides.¹³ Furthermore, these methods are generally limited in scope by the use of electrophilic sulfur reagents and/or strong bases and nucleophiles.

Recently, we reported a mild and stereoselective synthesis of the least stable isomeric (*Z*)-alkenes relying on the radical allylation of xanthates **3** with phenyl vinyl sulfones **1** (Scheme 1, *n* = 2).¹⁴ In the course of this study we observed in one experiment that the corresponding phenyl vinyl sulfide **2a** was also a competent substrate in this transformation (Scheme 1, *n* = 0).

Scheme 1. Experiments at the Origin of Our Study



Recognizing that our radical allylation could provide access to tetrasubstituted vinyl sulfides while at the same time overcoming the regioselectivity and functional group tolerance limitations encountered with established methods,¹⁵ we decided to study the scope of the reaction. Our results are reported herein.

We first examined the synthesis of trisubstituted vinyl sulfides by reacting various fluoropyridyl ethers **2**, derived from aldehydes and phenyl vinyl sulfide, with electro- and nucleophilic radicals (Figure 1).¹⁶

The reaction proved general, and in all cases, the targeted trisubstituted vinyl sulfides **5** were obtained in good yields, albeit with moderate stereoselectivities (Figure 1).

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(12) For other approaches, see: (a) Rao, S. A.; Knochel, P. *J. Am. Chem. Soc.* **1991**, *113*, 5735. (b) Comasseto, J. V.; Menezes, P. H.; Stefani, H. A.; Zeni, G.; Braga, A. L. *Tetrahedron* **1996**, *52*, 9687. (c) Fujimoto, T.; Hotei, Y.; Takeuchi, H.; Tanaka, S.; Ohta, K.; Yamamoto, I. *J. Org. Chem.* **1991**, *56*, 4799. (d) De Lucchi, O.; Modena, G. *J. Chem. Soc., Chem. Commun.* **1982**, 914.

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(15) Despite recent progress, hydrothiolation methods still suffer from the lack of regioselectivity. Cross-coupling reactions are severely limited by the poor access to the vinylic partner. Reactions involving electrophilic sulfur reagents are not compatible with the presence of other insaturations in the substrate.

(16) The fluoropyridyl ethers **2** were easily prepared by addition of the lithium anion derived from phenyl vinyl sulfide to aldehydes or ketones followed by nucleophilic aromatic substitution of 2,6-difluoropyridine. See Supporting Information for details.

(17) Measures of the energies necessary for monosubstituted cyclohexanes to equilibrate between their most stable and their least stable conformations are reported in the literature; see: Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*; John Wiley & Sons, Inc.: New York, NY, 2001; p 443. These “*A*” values can be considered as an approximate representation of the steric bulk of a given group. For instance $A_{(\text{SPh})} = 0.8 \text{ kcal} \cdot \text{mol}^{-1} < A_{(\text{Me})} = 1.70 \text{ kcal} \cdot \text{mol}^{-1}$.

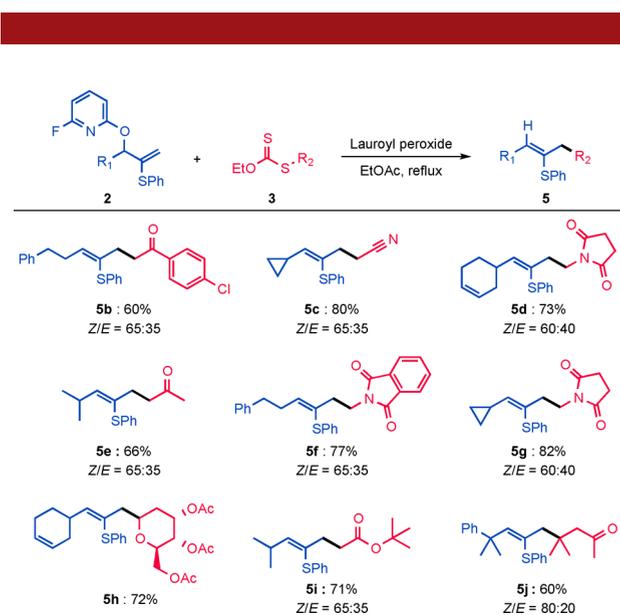


Figure 1. Scope of the radical allylation for the synthesis of trisubstituted vinyl sulfides. Reaction conditions: olefin **2** (2 equiv), xanthate **3** (1 equiv); lauroyl peroxide was added in 20 mol %/h portions (with respect to the xanthate). **5h** was obtained as a mixture of diastereo- and geometric isomers, but the *Z/E* ratio could not be determined by ¹H NMR analysis. For **5j**, lauroyl peroxide was added in 30 mol %/h portions.

We believe that the preferential formation of the (*Z*)-isomer is due to the relative smallness of the SPh substituent compared to standard alkyl groups.¹⁷ As suggested by the remarkably high yielding formation of vinyl sulfides **5d** and **5h** and by our recent study on polar effects in radical fragmentations,¹⁸ the elimination step is significantly faster in the case of vinyl sulfides than in the case of vinyl sulfones.¹⁹ This comparatively rapid elimination may also account for the modest selectivities observed by preventing the intermediate adduct radical from completely adopting its most stable conformation prior to fragmentation.

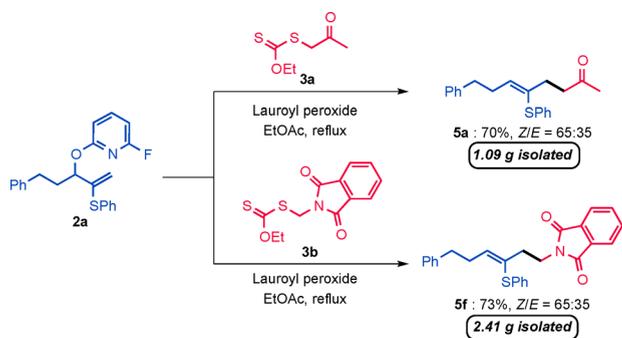
The robustness of this radical allylation is further demonstrated by the gram scale synthesis of vinyl sulfides **5a** and **5f** (Scheme 2). Indeed, the procedure routinely used on the 0.5–1.0 mmol scale delivered **5a** and **5f** in nearly identical yields when applied on the 5 and 8 mmol scale respectively.

We were encouraged by these first results to further expand this radical addition–elimination process to tetrasubstituted thio-enol ethers. Indeed, tetrasubstituted vinyl sulfides could be assembled in good yield and moderate (*Z*)-selectivity as shown by examples displayed in Table 2. The formation of vinyl sulfides bearing acid sensitive functions such as a masked unsaturated aldehyde **5l** or ketal **5n** as well as the tolerance for insaturations (alkenes **5d**, **5h**, and **5o**, enone **5x**, Figures 1 and 2) and base/nucleophile

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(19) For instance, no competing 5-*exo*-trig cyclization of the intermediate adduct radical was observed in the case of **5d** and **5h**. Furthermore, the reaction of analogs of the olefin used to prepare **5d** and **5h**, bearing an electron-withdrawing CF₃ or SPh substituent instead of the electron-donating SPh group, gave complex mixtures.

Scheme 2. Robustness of the Radical Allylation



sensitive groups such as enones, ketones, esters, phthalimides, or succinimides testify to the mildness of this approach. Such functional groups would typically not be compatible with previous literature methods.¹³ Vinyl sulfides **5p** and **5w** were prepared by combining our earlier results with trifluoromethyl alkenes²⁰ with the present work. The synthesis of thio-enol ether **5w** nicely highlights the convergence of this route since the xanthate involved was itself made by an intermolecular addition of the *S*-(1-cyano-1-methyl)ethyl xanthate to *N*-vinylphthalimide (Figure 2).²¹ Complex structures may also be efficiently constructed in one step as shown by the formation of cortisone derived adduct **5x** in 68% isolated yield (Figure 2). Finally, as mentioned earlier, the process is easily scalable. Thus, tetrasubstituted vinyl sulfide **5m** could be obtained in 74% isolated yield on the gram scale (8.0 mmol, 2.3 g isolated).

It is important to note that the radical addition–elimination is in competition with the Claisen rearrangement of the substrates.²² This sigmatopic rearrangement is especially effective with 2-fluoropyridyl ethers derived from tertiary allylic alcohols and occurs even in refluxing ethyl acetate, as illustrated by the near-quantitative conversion of **2b** into **7** (Scheme 3).

Normally, the rearrangement of 2-allyloxypyridines requires much higher temperatures and furnishes mixtures of regioisomers.²³ We were fortunate that, in our case, this Claisen rearrangement was not too fast so as to prevent the radical process from taking place. In this respect, we found that shortening the reaction time by adding the peroxide in larger portions allows producing the desired tetrasubstituted thio-enol ethers in comparable yield to the less substituted analogs (Figure 2 vs 1).

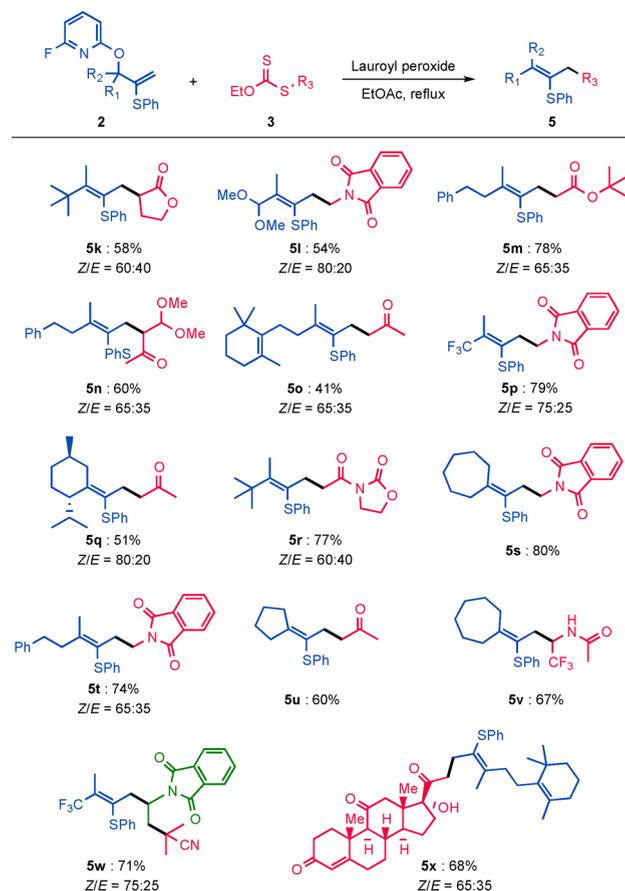


Figure 2. Scope of the radical allylation for the synthesis of tetrasubstituted vinyl sulfides. Reaction conditions: olefin **2** (2 equiv), xanthate **3** (1 equiv), lauroyl peroxide was added in 20 mol %/h portions (with respect to the xanthate). For **5p**, **5s**, **5u**, **5v**, **5w**, and **5x**, lauroyl peroxide was added in 40 mol %/h portions.

When the xanthate partner contains an α -carbonyl, then, the addition–fragmentation of the corresponding radical constitutes a formal synthesis of 1,4-dicarbonyls,²⁴ since vinyl sulfides are known to undergo hydrolysis upon treatment with various Lewis²⁵ or Brønsted²⁶ acids.

The products are in fact extremely useful as regioselectively monoprotected 1,4-dicarbonyls. For example, Cohen²⁷ used γ -keto vinyl sulfides to prepare *exo*-cyclopentenes derivatives and Hua exploited the cyclization of the thionium ions derived therefrom in the total synthesis of (+)-pentalene²⁸ and (+)-hirsutene.²⁹

(20) Debien, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 5118.

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(27) (a) Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569. (b) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106. (c) Deng, K.; Bensari-Bouguerra, A.; Whetstone, J.; Cohen, T. *J. Org. Chem.* **2006**, *71*, 2360. (d) Chen, W.; Zhao, X.; Lu, L.; Cohen, T. *Org. Lett.* **2006**, *8*, 2087.

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Scheme 3. Claisen Rearrangement of Precursor **2b**

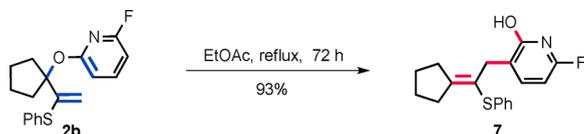
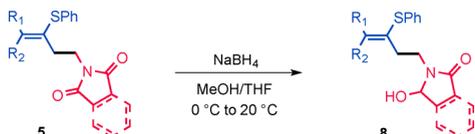


Table 1. Chemoselective Reduction of Succinimide and Phthalimide Containing Vinyl Sulfides



substrate	R ¹	R ²	substituent	yield	Z/E ^a
5d	cyclohex-3-en	H	succinimide	8a : 95%	60:40
5f^b	dihydrocinnamyl	H	phthalimide	8b : 90%	95:5
5g	cyclopropyl	H	succinimide	8c : 80%	65:35
5p^c	CF ₃	Me	phthalimide	8d : 93%	80:20 ^d
5s	cycloheptyl		phthalimide	8e : 96%	–

^a Z/E ratios of **5** and **8** were identical. ^b **5f** was obtained in a Z/E = 95:5 ratio by recrystallization of the Z/E = 65:35 mixture originally obtained. ^c The reaction was run in a 3:1 mixture of MeOH/DCM. ^d The (Z) and (E) isomers were separated by silica gel column chromatography.

In contrast, and to the best of our knowledge, vinyl sulfides have never been used as π -nucleophiles in reactions with the well-known and strongly electrophilic *N*-acylium cations.³⁰ Since our technology allows the ready assembly of the required substrates necessary for such transformations, we examined briefly this interesting synthetic extension. Thus, hemiaminals **8a–e** were prepared in good yield by reduction with NaBH₄ according to literature procedures (Table 1).³¹

We first subjected succinimide derived hemiaminals **8a** and **8c** to formic acid but only obtained complex mixtures.

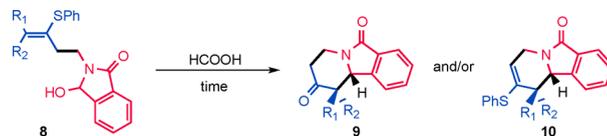
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(32) *(cis)*-**10b** proved remarkably robust and remained intact upon exposure to strong acids such as H₂SO₄ or HCl.

Table 2. Cyclization of Vinyl Sulfides on *N*-Acylium Ions^a



substrate	Z/E	time	yield 9	dr 9	yield 10	dr 10
8b	95:5	12 h	<i>(cis)</i> - 9a : 62%	≥95:5	10a : –	–
<i>(Z)</i> - 8d	≥95:5	2 days	<i>(cis)</i> - 9b : –	–	<i>(cis)</i> - 10b : 61%	95:5
<i>(E)</i> - 8d	≤95:5	2 days	<i>(trans)</i> - 9b : 70%	≥95:5	<i>(trans)</i> - 10b : –	–
8e	–	7 days	9c : 61%	–	10c : –	–
8e^b	–	10 min	9c : 20%	–	10c : 48%	–

^a Compounds **8** were dissolved in pure formic acid and stirred in an open to air flask. ^b Reaction ran in DCM with 4 Å molecular sieves.

However, hemiaminals **8b**, **8d**, and **8e** respectively derived from phthalimides **5f**, **5p**, and **5s** smoothly underwent cyclization to furnish tricyclic ketones **9** and/or vinyl sulfides **10** (Table 2). These reactions proved efficient for both tri- and tetrasubstituted vinyl sulfides, even those bearing a bulky or an electron withdrawing CF₃ group. They also turned out to be highly stereoselective, as shown by examples (*cis*)-**9a**, (*cis*)-**10b**, and (*trans*)-**9b**. Amusingly, trifluoromethyl alkene (*Z*)-**8d** selectively gave vinyl sulfide (*cis*)-**10b**³² while (*E*)-**8d** furnished ketone (*trans*)-**9b** arising from hydrolysis of the corresponding (*trans*)-thio-enol ether. In the case of hemiaminal **8e** we also found that prolonged exposure to formic acid provided ketone **9c** while a short treatment with formic acid in the presence of 4 Å molecular sieves gave vinyl sulfide **10c** as the major product.

In conclusion, we have developed a flexible, mild, and operationally simple synthesis of regio-defined tri- and tetrasubstituted vinyl sulfides. The ability to rapidly bring together various functional groups that could then be made to react with the thio-enol ether is illustrated by the assembly of polycyclic nitrogen heterocycles through cyclization with *in situ* generated *N*-acylium species. Numerous other variations and modifications can be readily conceived and hopefully eventually implemented.

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Supporting Information Available. Experimental procedures and characterization spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.