ORGANIC LETTERS

2012
Vol. 14, No. 13
3526–3529

Intramolecular Alkene Electrophilic Bromination Initiated *ipso*-Bromocyclization for the Synthesis of Functionalized Azaspirocyclohexadienones

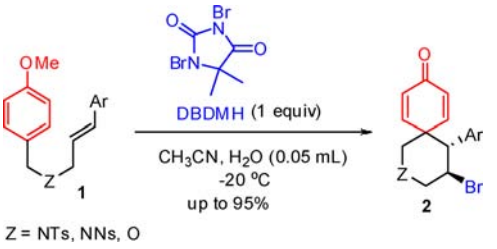
Qin Yin and Shu-Li You*

State Key Laboratory of Organometallic Chemistry Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

slyou@sioc.ac.cn

Received June 4, 2012

ABSTRACT



Intramolecular alkene electrophilic bromination initiated dearomative cyclization has been realized in the presence of DBDMH to provide functionalized azaspirocyclohexadienones in excellent yields under mild conditions.

Spirocycles have attracted great attention in organic synthesis because of the challenge toward their synthesis and their extensive existence as a key structural unit in functional molecules. Among them, azaspirocyclohexadienones are of particularly significant importance in organic synthesis (Figure 1).[1] To date, various methods have been developed to construct this core motif, including intramolecular cyclization reactions such as radical cyclization,[2] electrophilic substitution on *N*-acyliminium or thionium ions,[3] metal-catalyzed (Pd, Ir, Ru, Cu) dearomatization reactions,[4] methods based on hypervalent iodine reagents,[5] an *ipso*-Friedel–Crafts/Michael addition cascade strategy,[6] and others.[7] However, many of the reported methods were restricted to relatively harsh reaction conditions, a limited

(1) For reviews, see: (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (b) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165. (c) Rosenberg, S.; Leino, R. *Synthesis* **2009**, 2651.

(2) For recent representative examples, see: (a) González-López de Turiso, F.; Curran, D. P. *Org. Lett.* **2005**, *7*, 151. (b) Ibarra-Rivera, T.; Gámez-Montaño, R.; Miranda, L. D. *Chem. Commun.* **2007**, 3485. (c) Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 9439. (d) Lanza, T.; Minozzi, M.; Monesi, A.; Nanni, D.; Spagnolo, P.; Zanardia, G. *Adv. Synth. Catal.* **2010**, *352*, 2275. (e) Gámez-Montaño, R.; Ibarra-Rivera, T.; Kaïm, L. E.; Miranda, L. D. *Synthesis* **2010**, 1285.

(3) (a) Casimir, J. R.; Tourwé, D.; Iterbeke, K.; Guichard, G.; Briand, J.-P. *J. Org. Chem.* **2000**, *65*, 6487. (b) Ovens, C.; Martin, N. G.; Procter, D. J. *Org. Lett.* **2008**, *10*, 1441. (c) Glushkov, V. A.; Stryapunina, O. G.; Gorbunov, A. A.; Maiorova, O. A.; Slepukhin, P. A.; Ryabukhina, S. Y.; Khorosheva, E. V.; Sokol, V. I.; Shklyaev, Y. V. *Tetrahedron* **2010**, *66*, 721.

(4) (a) Pigge, F. C.; Coniglio, J. J.; Rath, N. P. *Org. Lett.* **2003**, *5*, 2011. (b) Pigge, F. C.; Dhanya, R.; Hoefgen, E. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 2887. (c) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (d) Nemoto, T.; Ishige, Y.; Yoshida, M.; Kohno, Y.; Kanematsu, M.; Hamada, Y. *Org. Lett.* **2010**, *12*, 5020. (e) Matsuura, B. S.; Condie, A. G.; Buff, R. C.; Karahalis, G. J.; Stephenson, C. R. J. *Org. Lett.* **2011**, *13*, 6320. (f) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455.

(5) For recent representative examples, see: (a) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194. (b) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. *Tetrahedron* **2002**, *58*, 6285. (c) Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271. (d) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 6193. (e) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224. (f) Dohi, Y.; Minamitsuji, Y.; Maruyama, A.; Hirose, S.; Kita, Y. *Org. Lett.* **2008**, *10*, 3559. (g) Liang, J.; Chen, J.; Du, F.; Zeng, X.; Li, L.; Zhang, H. *Org. Lett.* **2009**, *11*, 2820. (h) Andrez, J.-C.; Giroux, M.-A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. (i) Dohi, T.; Nakae, T.; Ishikado, Y.; Kato, D.; Kita, Y. *Org. Biomol. Chem.* **2011**, *9*, 6899. (j) Desjardins, S.; Andrez, J.-C.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406.

10.1021/ol301531z
Published on Web 06/22/2012

substrate scope, and expensive catalytic systems. Recently, intramolecular electrophilic *ipso*-halocyclization of alkynes[8] has emerged as an important method for the construction of spiro-carbocycles and heterocycles, allowing facile installation of a halo group and quaternary spirocenter. This method, to our knowledge, is limited to substrates containing an alkyne group and has not yet been expanded to alkene substrates. On the other hand, the functionalization of alkenes represents a commonly employed strategy for the construction of molecular complexity in organic synthesis. Catalytic enantioselective olefin halocyclization reactions such as halo-*O*-cyclizations (e.g., lactonization, etherification) and halo-*N*-cyclizations (e.g., lactamization, aminocyclization) have gained rapid development in recent years.[9] However, an intramolecular halo-*C*-spirocyclization procedure based on alkene group has not been reported to date.[10]

We envisaged that suitable *para*-alkene substituted anisole derivatives (**1**) under electrophilic halogenation initiated dearomative spirocyclization would provide functionalized azaspirocyclohexadienones (Scheme 1). In this paper, we report such an efficient synthesis of highly functionalized azaspirocyclohexadienones *via* the intramolecular alkene electrophilic bromination initiated *ipso*-bromocyclization.

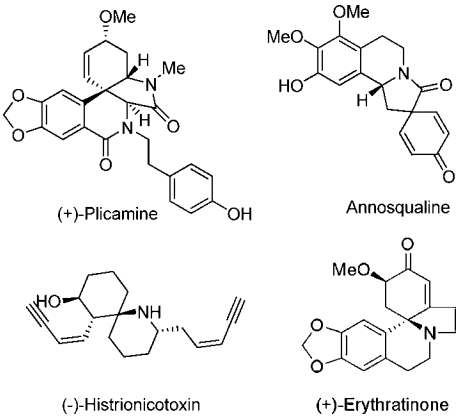
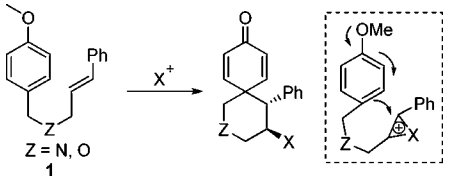


Figure 1. Representative azaspirocycle-based nature products.

Scheme 1. Proposed Electrophilic Halogenation Initiated Dearomative Spirocyclization



We began our exploration by testing model substrate **1a** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the halide electrophile. To our delight, the reaction in dichloromethane at rt proceeded very fast (<5 min) to afford the desired product **2a** in 20% yield (entry 1, Table 1). The anti stereochemistry of product **2a** was established by X-ray analysis (see the Supporting Information). The reaction at -20 °C was found to afford a much improved yield (72%, entry 2, Table 1). As summarized in Table 1, several halide electrophiles were further evaluated in this reaction. Compared to the high activity of DMDBH, other halide electrophiles such as *N*-bromoacetamide, DCDMH, and NIS gave low conversions even at rt (entries 3–6, Table 1).

With DBDMH as the halide electrophile, the reaction conditions were further optimized. The results are summarized in Table 2. Various solvents ($CHCl_3$, DCE, toluene, CF_3CH_2OH, CH_3CN) were tested, and all led to the formation of the desired azaspirocyclohexadienone (entries 1–6, Table 2). The reaction in CH_3CN gave the best yield (entry 6, Table 2). Elevating the reaction temperature to 0 °C caused a slightly decreased yield (70%, entry 7, Table 2). Then different additives such as 4 Å MS, a Brønsted acid, a base, and KBr (entries 7–12, Table 2)

(6) Rodríguez-Solla, H.; Concellón, C.; Tuya, P.; García-Granda, S.; Díaz, M. R. *Adv. Synth. Catal.* **2012**, *354*, 295.

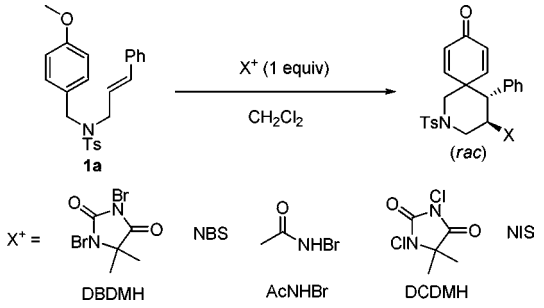
(7) For recent representative examples, see: (a) Swenton, J. S.; Carpenter, K.; Chen, Y.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem.* **1993**, *58*, 3308. (b) Hares, O.; Hobbs-Mallyon, D.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 148. (c) Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933. (d) Warrener, R. N.; Liu, L.; Russell, R. A.; Tiekink, E. R. T. *Synlett* **1998**, 387. (e) Liu, L.; Wang, Z.; Zhao, F.; Xi, Z. *J. Org. Chem.* **2007**, *72*, 3484.

(8) For recent representative examples, see: (a) Appel, T. R.; Yehia, N. A. M.; Baumeister, U.; Hartung, H.; Kluge, R.; Ströhl, D.; Fanghänel, E. *Eur. J. Org. Chem.* **2003**, 47. (b) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230. (c) Tang, B.-X.; Yin, Q.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2008**, *73*, 9008. (d) Yu, Q.-F.; Zhang, Y.-H.; Yin, Q.; Tang, B.-X.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2008**, *73*, 3658. (e) Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1063. (f) Tang, B.-X.; Zhang, Y.-H.; Song, R.-J.; Tang, D.-J.; Deng, G.-B.; Wang, Z.-Q.; Xie, Y.-X.; Xia, Y.-Z.; Li, J.-H. *J. Org. Chem.* **2012**, *77*, 2837.

(9) For recent representative examples, see: (a) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (b) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874. (c) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (d) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (e) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (f) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (g) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (h) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655. (i) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474. (j) Yousefi, R.; Whitehead, D. C.; Mueller, J. M.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 608. (k) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2738. (l) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (m) Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2593. (n) Lozano, O.; Blessley, G.; Martinez del Campo, T.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 8105. (o) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860. (p) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (q) Zhang, W.; Liu, N.; Schienebeck, C. M.; Decloux, K.; Zheng, S.; Werness, J. B.; Tang, W. *Chem.—Eur. J.* **2012**, *18*, 7296. (r) Tan, C. K.; Le, C.; Yeung, Y.-Y. *Chem. Commun.* **2012**, *48*, 5793. (s) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256. (t) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. (u) Chen, J.; Zhou, L.; Tan, C. K.; Yeung, Y.-Y. *J. Org. Chem.* **2012**, *77*, 999.

(10) Intramolecular halo-*C*-cyclizations of alkenes using malonate as the nucleophile have been reported; for account, see: Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191 and reference therein.

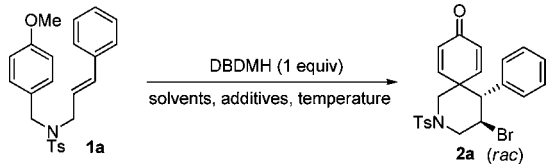
Table 1. Screening of Halide Electrophiles and Reaction Conditions Using **1a**



entry[a]	t (°C)	X^+	time	yield (%)[b]
1	rt	DBDMH	<5 min	20
2	−20	DBDMH	10 h	72
3	−20	NBS	48 h	15
4	rt	AcNHBr	20 h	trace
5	rt	DCDMH	72 h	trace
6	rt	NIS	72 h	trace

[a] Reactions were performed with **1a** (0.1 mmol), X^+ (1.1 equiv). [b] Isolated yield.

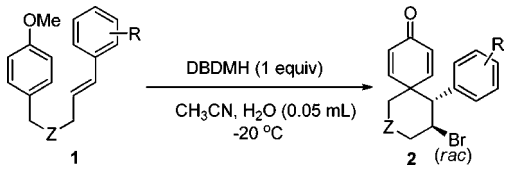
Table 2. Screening of Solvents, Additives, and Temperature



entry[a]	solvent	t (°C)	additive	time (h)	yield (%)[b]
1	CH_2Cl_2	−20	/	10	72
2	$CHCl_3$	−20	/	24	73
3	toluene	−20	/	48	45
4	DCE	−20	/	10	71
5	CF_3CH_2OH	−20	/	72	35
6	CH_3CN	−20	/	0.2	80
7	CH_3CN	0	/	0.1	70
8	CH_3CN	−20	4 Å MS	0.1	58
9	CH_3CN	−20	BzOH (10 mol %)	0.4	30
10	CH_3CN	−20	DBACO (20 mol %)	15	56
11	CH_3CN	−20	$NaHCO_3$ (1 equiv)	0.3	45
12	CH_3CN	−20	KBr (1 equiv)	0.2	45
13	CH_3CN	−20	H_2O (0.05 mL)	0.5	91
14	CH_3CN	−20	H_2O (0.1 mL)	0.5	90

[a] Reactions were performed with **1a** (0.1 mmol), DBDMH (1.1 equiv). [b] Isolated yield.

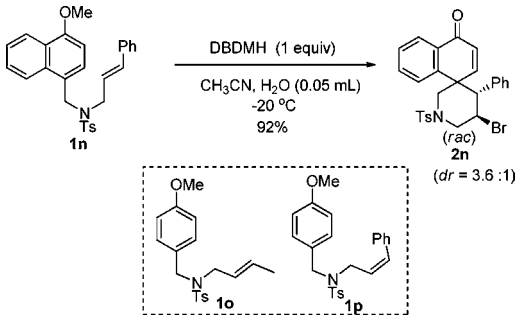
Table 3. Substrate Scope



entry[a]	Z	**1**, R	product	yield (%)[b]
1	NTs	**1a**, H	**2a**	91
2	NTs	**1b**, 2-Me	**2b**	84
3	NTs	**1c**, 4-Me	**2c**	93
4	NTs	**1d**, 4-MeO	**2d**	68
5	NTs	**1e**, 2-Cl	**2e**	93
6	NTs	**1f**, 3-Cl	**2f**	85
7	NTs	**1g**, 4-Cl	**2g**	91
8	NTs	**1h**, 2-Br	**2h**	94
9	NTs	**1i**, 4-Br	**2i**	92
10	NTs	**1j**, 3-NO_2	**2j**	90
11	NTs	**1k**, 4-CO_2Me	**2k**	95
12	NNs	**1l**, H	**2l**	93
13	O	**1m**, H	**2m**	89

[a] Reactions were performed with 1 (0.1 mmol), DBDMH (1.1 equiv). [b] Isolated yield.

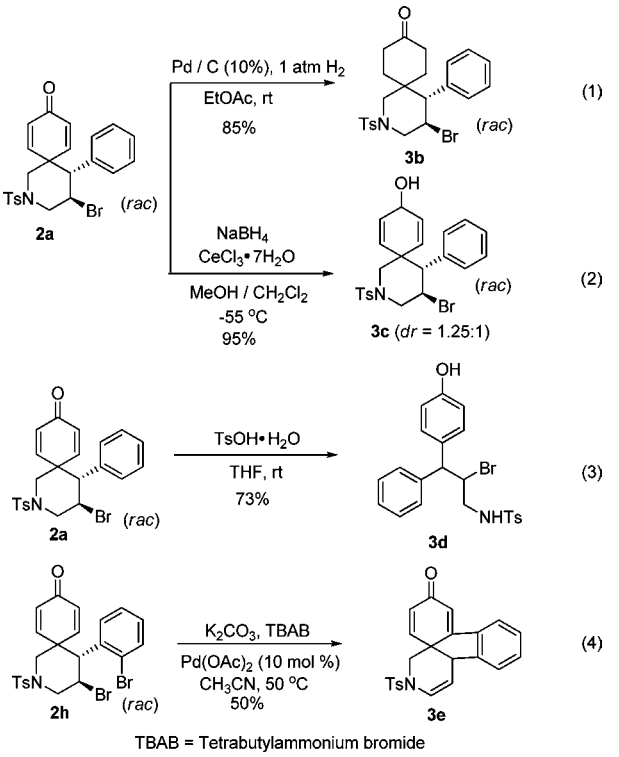
Scheme 2. Extension of the Substrate Scope



were tested; however, none of them displayed positive effects on the reaction outcome. Finally, to our delight, water was found to be an effective additive, and the reaction with 0.05 mL of water could lead to a 91% yield (entry 13, Table 2). Increasing the amount of water further did not improve the yield (entry 14, Table 2).

With the optimized reaction conditions in hand, the scope of the *ipso*-halocyclization reaction was explored. The results are summarized in Table 3. For the alkene substituted phenyl ring, either an electron-donating group (2-Me, 4-Me, 4-MeO, 6-BnO) or an electron-withdrawing group (2-Cl, 3-Cl, 4-Cl, 2-Br, 4-Br, 3-NO_2, 4-CO_2Me) could be well tolerated. In most cases, good to excellent yields were achieved (68−95%, entries 2−11, Table 3). For the protection group on the *N*-linkage, when 4-nitrobenzene sulfonyl (Ns) was used, a 93% yield was obtained (entry 12, Table 3). Notably, when the *N*-linker was replaced with an *O*-linker, the *ipso*-halocyclization reaction also proceeded

Scheme 3. Transformations of the Products



well to afford oxospirocyclohexadienone in 89% yield (entry 13, Table 3).

To further examine the substrate scope, naphthalene skeleton-based substrate **1n** was tested (Scheme 2). The reaction proceeded smoothly to afford the desired product **2n** in 92% yield (*dr* = 3.6:1). Methyl substituted alkene substrate **1o** and *cis*-alkene substrate **1p** were also tested, however, no dearomatiztion product was isolated.

The products obtained by this intramolecular electrophilic *ipso*-halocyclization reaction could be subjected to various transformations. As shown in Scheme 3, from treatment of azaspirocyclohexadienone **2a** under different reduction conditions, chemoselective reduction could be realized (eqs 1 and 2). Under Pd/C hydrogenation conditions, the two double bonds were hydrogenated, while the ketone moiety was converted to alcohol by Luche reduction. When **2a** was treated with *p*-toluenesulfonic acid, a fragmentation product **3d** was isolated in 73% yield (eq 3). This fragmentation occurs *via* a retro-Mannich reaction catalyzed by acid and then hydrolysis of the resulted *N*-Ts iminium ion.[3b,11] In addition, the intramolecular Heck reaction could be conducted with **2h** under conditions utilizing $Pd(OAc)_2$ and TBAB, providing azaspirotricyclic product **3e** in moderate yield (eq 4).[8f]

In summary, we have developed an efficient method to provide functionalized azaspirocyclohexadienones *via* intramolecular alkene electrophilic bromination initiated dearomative cyclization. The method features a wide substrate scope, a high yield, and mild conditions. The products obtained here are compatible with various transformations.

Acknowledgment. We thank the National Basic Research Program of China (973 Program 2009CB825300), the National Natural Science Foundation of China (20923005, 21025209, 21121062), and the Chinese Academy of Sciences for generous financial support.

Supporting Information Available. Detailed experimental procedures and spectroscopic data for all new compounds and X-ray crystal data of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) (a) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256. (b) Yokosaka, T.; Nemoto, T.; Hamada., Y. *Chem. Commun.* **2012**, *48*, 5431.

The authors declare no competing financial interest.