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Synthesis of Differentially Substituted 1,2-Diamines through Advances in C–H Amination Technology

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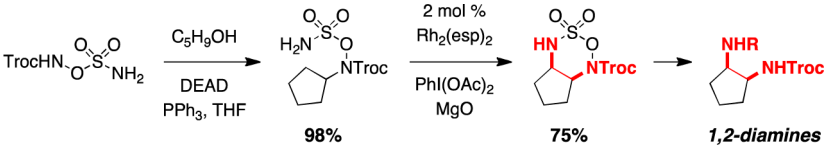
ABSTRACT



A general, high yielding method for the synthesis of 1,2-diamine derivatives is described that capitalizes on selective, rhodium-catalyzed C–H insertion of hydroxylamine-based sulfamate esters. The resulting Troc-protected oxathiadiazinane heterocycles are easily modified and can be reduced under the mild action of NaI to afford differentially substituted diamine products. This technology offers a number of salient improvements over related C–H and π-bond amination tactics for diamine synthesis.

Vicinal diamines, particularly those with non-equivalent nitrogen substitution, appear as ubiquitous structural elements in designed molecules and natural products (Figure 1).[1] Such compounds enjoy far-ranging application in areas that include materials science,[2] catalysis and coordination chemistry,[3] and medicinal chemistry.[4] The lack of convenient methods for the preparation of 1,2-diamine derivatives, however, remains a problem in synthesis,[5] complicated by an unavoidable reliance on serial functional group interconversion. The application of C–H amination technology for 1,2-diamine assembly can, in principle, streamline access to such structures.[6,7] Our efforts to delineate a general solution for preparing differentially substituted 1,2-diamines have led to the identification of a novel family of N-protected hydroxylamine sulfamates that react under the action of a dirhodium catalyst to give

(1) For examples of differentially substituted diamines, see: (a) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941–6944. (b) Roszkowski, P.; Maurin, J.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 1415–1419. (c) Garah, F. B. E.; Stigliani, J. L.; Coslédan, F.; Meunier, B.; Robert, A. *ChemMedChem* **2009**, *4*, 1469–1479. (d) Qiao, J. X. J.; Chang, C. H. C.; Cheney, D. L. D.; Morin, P. E. P.; Wang, G. Z. G.; King, S. R. S.; Wang, T. C. T.; Rendina, A. R. A.; Luettgen, J. M. J.; Knabb, R. M. R.; Wexler, R. R. R.; Lam, P. Y. S. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4419–4427. (e) El-Latif, N. A. A.; Abdulla, M. M.; Amr, A. E.-G. E. *Acta Pharm.* **2008**, *58*, 43–59. (f) Brouillette, W. J.; Bajpai, S. N.; Ali, S. M.; Velu, S. E.; Atigadda, V. R.; Lommer, B. S.; Finley, J. B.; Luo, M.; Air, G. M. *Bioorg. Med. Chem.* **2003**, *11*, 2739–2749.

(2) For select examples of diamines used in materials science, see: (a) Lee, L. H.; Chen, W. C. *Polymer* **2005**, *46*, 2163–2174. (b) Li, X. G.; Huang, M. R.; Duan, W.; Yang, Y. L. *Chem. Rev.* **2002**, *102*, 2925–3030. (c) Cheng, L.; Jian, X. G.; Mao, S. Z. *J. Polym. Sci.* **2002**, *40*, 3489–3496.

(3) For select examples of diamines used in asymmetric synthesis, see: (a) De Parrodi, C. A.; Juaristi, E. *Synlett* **2006**, *17*, 2699–2715. (b) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 167–170. (c) Cimarelli, C.; Fratoni, D.; Palmieri, G. *Tetrahedron: Asymmetry* **2009**, *20*, 2234–2239. (d) Nakayama, K.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 17666–17667. (e) Kizirian, J. C. *Chem. Rev.* **2008**, *108*, 140–205.

(4) For select examples of medicinally relevant dimine-derived structures, see: (a) Michalson, E. T. E.; Szmuszkovicz, J. J. *Prog. Drug Res.* **1989**, *33*, 135–149. (b) DeMong, D. E.; Williams, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 8561–8565. (c) Rane, D. F.; Girijavallabhan, V. M.; Ganguly, A. K.; Pike, R. E.; Saksena, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 3201–3204. (d) Costello, G. F. G.; Main, B. G. B.; Barlow, J. J. J.; Carroll, J. A. J.; Shaw, J. S. J. *Eur. J. Pharmacol.* **1988**, *151*, 475–478. (e) Day, T. A. T.; Bennett, J. L. J.; Pax, R. A. R. *Parasitol. Today* **1992**, *8*, 342–344.

(5) For synthetic approaches toward 1,2-diamines, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627. (b) Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101–114. (c) De Figueiredo, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190–1193. (d) Savoia, D. *Top. Organomet. Chem.* **2005**, *15*, 1–58. (e) Muñiz, K. *New J. Chem.* **2005**, *29*, 1371–1385. (f) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151–153. (g) Mortensen, M. S.; O'Doherty, G. A. *Chemtracts: Org. Chem.* **2005**, *18*, 555–561. (h) Du, H.; Yuan, W.; Zhao, B. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689. (i) Yuan, W.; Du, H.; Zhao, B.; Shi, Y. *Org. Lett.* **2007**, *9*, 2589–2591. (j) Chong, A. O.; Oshima, K.; Sharpless, K. *J. Am. Chem. Soc.* **1977**, *99*, 3420–3426. (k) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269–275. (l) Zhao, B.; Peng, X.; Zhu, Y.; Ramirez, T. A.; Cornwall, R. G.; Shi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20890–20900. (m) Chávez, P.; Kirsch, J.; Streuff, J.; Muñiz, K. *J. Org. Chem.* **2012**, *77*, 1922–1930.

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[1,2,3,6]-oxathiadiazinane-2,2-dioxide heterocycles.[8] Herein, we describe the synthesis and unique properties of *N*-Troc-derived oxathiadiazinanes as masked 1,2-diamine equivalents. This chemistry offers a general method for vicinal diamine preparation in a minimal number of steps from simple alcohol starting materials.

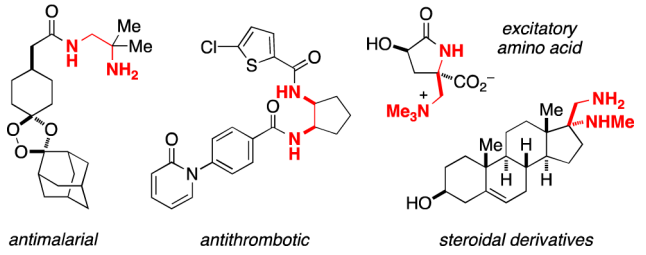


Figure 1. 1,2-Diamine derivatives as a recurring structural motif in biologically active, naturally occurring and designed molecules.

In considering the potential utility of C−H amination for the preparation of substituted 1,2-diamine products, our earliest efforts focused on the development of intramolecular oxidative cyclization of urea substrates.[9] Such compounds were found to engage in dirhodium-mediated amination to afford imidazolin-2-one heterocycles. The stability of these products toward hydrolysis, coupled with the somewhat restricted substrate range of the C−H amination process, prompted subsequent investigations to identify alternative nitrogen sources that would (1) engage in C−H amination reactions with functionally rich starting materials and (2) afford heterocyclic products that could be easily modified and cleaved to give the desired *vic*-diamines. Hydroxylamine-based sulfamate esters appear to satisfy both of these requirements (Figure 2).[10]

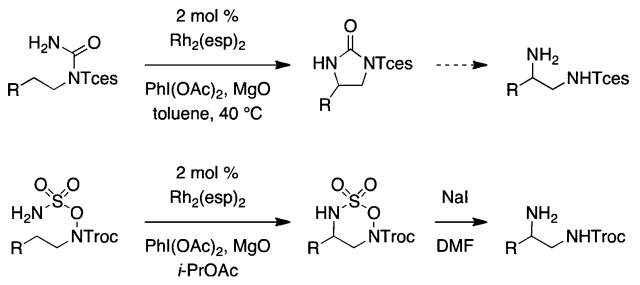


Figure 2. Access to differentially substituted vicinal diamine products is facilitated through directed C−H amination to form oxathiadiazinane heterocycles. Tces = 2,2,2-trichloroethoxysulfonyl; Troc = 2,2,2-trichloroethoxycarbonyl.

Reagents of the general form $RNHSO_2NH_2$ in which R is either a sulfonyl or carbamoyl group are accessible in multigram quantities from hydroxylamine hydrochloride. These sulfamate derivatives react with 1° and 2° alcohols under Mitsunobu conditions to give substrates suitable for C−H amination. The choice of R group influences the performance of $RNHSO_2NH_2$ in the displacement reaction, as evidenced in Table 1. Treatment of cyclohexylmethanol with either $MbsNHOSO_2NH_2$ or $TrocNHOSO_2NH_2$ leads efficiently (> 85%) to the respective sulfamate derivatives. By contrast, use of the analogous N-Boc reagent results in a decreased yield of **1** due to competing formation of the regioisomeric N-alkylated material (2:1 mixture of N- and N′-products). It appears that a large differential acidity between the NH protons in these sulfamate nucleophiles is necessary for optimal performance in the Mitsunobu process.

For substrates such as **1**, we have found that the efficiency of the Rh-catalyzed C−H insertion reaction is dependent on the choice of hydroxylamine protecting group (Table 1). Tertiary and benzylic substrates derived from $MbsNHSO_2NH_2$ can be oxidized with 2 mol % $Rh_2(esp)_2$ and $PhI(OAc)_2$ in modest to high yields. These starting materials show a strong bias toward six-membered ring formation, as noted with other sulfamate derivatives.[10,11] Analogous N-Boc structures perform poorly, generally giving products in low to modest yields and returning variable amounts of unreacted starting material. Attempts to optimize C−H amination with the N-Boc substrate class by changing solvent conditions, catalyst, and reaction temperature have met with limited success.

N-Troc-protected hydroxylamine sulfamates can be oxidized efficiently in the presence of a dirhodium catalyst and $PhI(OAc)_2$ to furnish oxathiadiazinanes across a range of different structural types (Table 2). Oxidative cyclization

(6) For recent reviews on C−H amination, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (b) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379–3394. (c) Fantauzzi, S.; Caselli, A.; Gallo, E. *Dalton Trans.* **2009**, 5434–5443. (d) Collet, F.; Dodd, R.; Dauban, P. *Chem. Commun.* **2009**, 5061–5074. (e) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347–378. (f) Li, Z.; Capretto, D.; He, C. Silver-Catalysed Nitrene Transfer Reactions. In *Silver in Organic Chemistry*; Harmata, M., Ed.; Wiley: New York, 2010; pp 167−182. (g) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926–36.

(7) For select reports on C−H amination, see: (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379. (b) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639–642. (c) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500–7501. (d) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184–5186. (e) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825–6828. (f) Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2777–2779. (g) King, E.; Betley, T. *Inorg. Chem.* **2009**, *48*, 2361–2363. (h) Nörder, A.; Herrmann, P.; Herdtweck, E.; Bach, T. *Org. Lett.* **2010**, *12*, 3690–3692. (i) Lu, H.; Tao, J.; Jones, J. E.; Wojtas, L.; Zhang, X. P. *Org. Lett.* **2010**, *12*, 1248–1251. (j) Wiese, S.; Badiei, Y. M.; Gephart, R. T.; Mossin, S.; Varonka, M. S.; Melzer, M. M.; Meyer, K.; Cundari, T. R.; Warren, T. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 8850–8855. (k) Lyaskovskyy, V.; Suárez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011**, *133*, 12264–12273. (l) Harvey, M. E.; Musaev, D. G.; Du Bois, J. *J. Am. Chem. Soc.* **2011**, *133*, 17216. (m) Q. Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *133*, 2547–2550 and references therein.

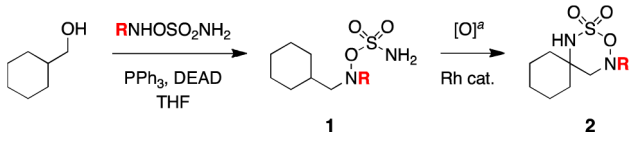
(8) We refer to these compounds as oxathiadiazinanes for convenience. We are aware of only one report of such compounds prior to our studies; see: Arfaei, A.; Smith, S. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1791–1794.

(9) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076.

(10) Olson, D. E.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 11248–11249.

(11) $Rh_2(esp)_2$ = $Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate)$_2$ and is commercially available from Aldrich.

Table 1. Evaluating N-Activating Groups for Both Mitsunobu Coupling and C−H Amination Reactions



entry[a]	R group	yield **1**	solvent	conversion **2**[b]
1	Mbs	**97**	PhH	**100 (99)**
2	Boc	**52**	PhH	**29 (–)**
3	Boc	–	^{i}PrOAc	**76 (–)**
4	Troc	**88**	^{i}PrOAc	**100 (88)**

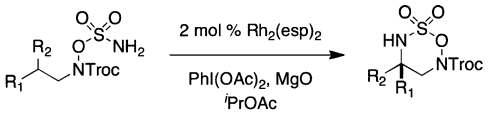
[a] Amination reactions were performed with 2 mol % $Rh_2(esp)_2$, 1.1 equiv of $PhI(OAc)_2$, and 2.3 equiv of MgO. [b] Product conversion estimated by ^{1}H NMR integration of the unpurified reaction mixture. Values in parentheses represent isolated product yields following chromatography on silica gel.

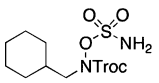
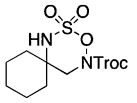
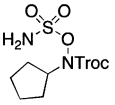
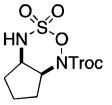
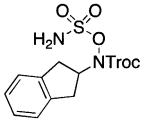
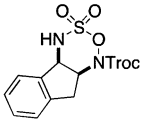
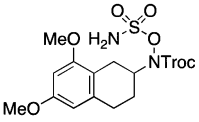
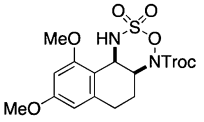
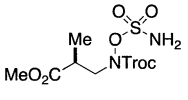
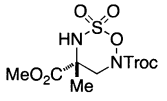
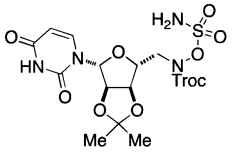
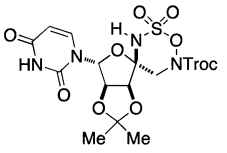
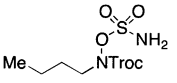
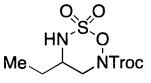
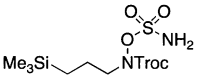
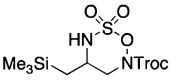
of substrates possessing 3°, benzylic, ethereal, and 2° C−H centers matches or exceeds the performance of the analogous Mbs-derivatives.[12] Additionally, the Troc heterocycles may be purified using standard chromatographic or crystallization techniques and are stable to subsequent manipulations (*vide infra*). Mbs-substituted oxathiadiazinanes are prone to unusual base-mediated fragmentation reactions, which can complicate purification, reduce isolated product yields, and prevent any modification of the heterocycle except for reductive ring opening.[13] N-Troc oxathiadiazinanes suffer none of these liabilities.

The potential utility of our diamination method is perhaps best illustrated with the cyclopentyl-derived sulfamate depicted in entry 2 (Table 2). C−H amination reactions of carbamates and ureas derived from 2° cycloalkanols generally fail to give even trace product.[14] The cyclopentyl sulfamate, however, affords the desired insertion product as a crystalline solid in 75% yield, a compound that can be readily processed to the corresponding diamine (see Figure 4). This particular insertion reaction has been performed on >1 g scale with no dimunition in yield. Similarly, we have prepared a related diamine derivative from 2-indanol (entry 3). In this example, the analogous Mbs-substituted oxathiadiazinane could not be isolated due to its intrinsic instability.

The oxidation of unfunctionalized 2° methylene centers in acyclic substrates is often complicated by poor catalyst turnover numbers and low isolated product yields. This point is exemplified with the *n*-butyl-derived substrate

Table 2. Oxidative Cyclization of N-Troc Hydroxylamine-Derived Sulfamate Esters



entry[a]	substrate	product	yield[b]
1			88
2			75
3			81[c]
4			83[c]
5			61
6			71
7			25[d]
8			73

[a] Reactions were performed in ^{i}PrOAc using 2 mol % $Rh_2(esp)_2$, 1.1 equiv of $PhI(OAc)_2$, and 2.3 equiv of MgO. [b] Isolated yield of product following chromatography on silica gel, except where noted. [c] Product isolated by filtration of the reaction mixture; see Supporting Information for details. [d] Value represents product conversion based on ^{1}H NMR integration of the unpurified reaction mixture.

shown in entry 7. Mechanistic evidence for related sulfamate oxidation reactions suggests that insertion proceeds through a concerted asynchronous transition state.[15] In principle, judicious placement of a silyl substituent one carbon removed from this center could impact the overall efficiency of the amination process by stabilizing charge polarization in the transition structure. This effect has been

(12) In general, Rh-catalyzed oxidations of Troc-protected substrates are quite efficient. The product oxathiadiazinanes, however, are typically isolated in slightly lower yields than would be expected from ^{1}H NMR analysis of the unpurified reaction mixtures, a result that may stem from problems of solubility of these crystalline materials. In some cases, isolation of the pure crystalline product can be accomplished without recourse to chromatography. Details are provided in the Supporting Information.

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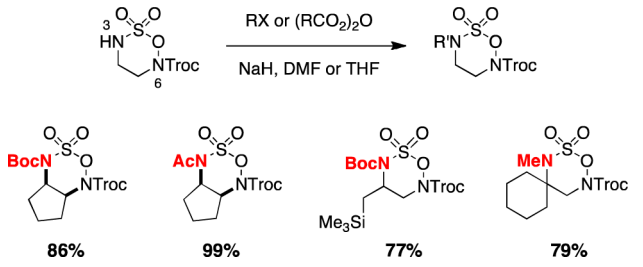


Figure 3. Troc-protected compounds are readily functionalized at the sulfamate nitrogen.

documented once prior in carbenoid C−H insertion chemistry and appears to translate to the Rh-catalyzed oxidation of sulfamate esters, as shown in entry 8.[16]

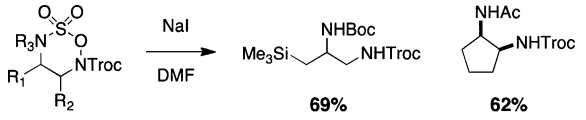
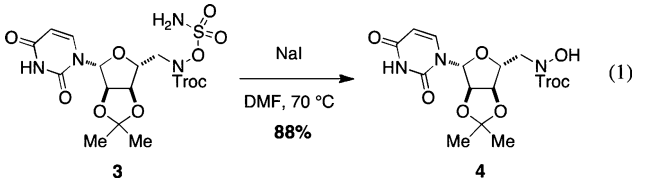


Figure 4. Mild reductive cleavage of oxathiadiazinanes yields differentially protected diamines.

Troc-protected oxathiadiazinanes may be easily modified at the N3 position under standard acylation or alkylation conditions (Figure 3). These results contrast rather markedly the chemistry of analogous Mbs-derived heterocycles, which fragment to liberate $MbsNH_2$ even under mild base treatment.[13] We have ascribed these differences in reactivity to subtle alterations in ring conformation influenced by the different N6 protecting groups; the mechanism(s) for N-Mbs oxathiadiazinane cleavage, however, remains opaque. In practice, the availability of N-Troc oxathiadiazinanes and their favorable reactivity with electrophilic reagents should expand the utility of this family of heterocycles for diamine synthesis.

Differentially modified 1,2-diamines can be accessed by mild N−O bond reduction. We have previously shown that hydrogenolytic N−O cleavage of Troc-protected oxathiadiazinanes is feasible with H_2 and catalytic Pd/C;[13a] competitive deprotection of the Troc-group, however, can sometimes interfere with the application of this method. This problem is completely avoided by utilizing NaI as a reducing agent (Figure 4). Under these conditions, the mixture of N-Troc oxathiadiazinane and I^- turns red, presumably due to the formation of I_2. This change in solution color provides a convenient indicator of reaction progress. The reaction of oxathiadiazinanes with I^- is one of only few reports demonstrating the use of this reagent for heteroatom bond reduction.[17] As evidence of the unique reactivity of N-Troc oxathiadiazinanes toward I^-, other hydroxylamine derivatives, such as uracil sulfamate **3**, fail to undergo N−O bond reduction when subjected to NaI, even at elevated temperatures. Instead, hydrolysis of the sulfamoyl group simply results in the formation of the corresponding hydroxylamine **4** (eq 1).



(1)

Troc-protected hydroxylamine-derived sulfamates are made available from alcohol starting materials and have proven to be effective substrates for Rh-catalyzed C−H insertion. Oxathiadiazinane products of varying complexity are formed in high yield, are stable to isolation and derivatization, and submit to mild reductive cleavage to afford value-added, differentially substituted diamine structures. All told, these findings should serve to advance C−H amination as a tool for chemical synthesis.

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

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The authors declare no competing financial interest.