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Stereocontrolled Synthesis of α-Amino-α′-alkoxy Ketones by a Copper-Catalyzed Cross-Coupling of Peptidic Thiol Esters and α-Alkoxyalkylstannanes

Hao Li,[†] Anyu He,[‡] John R. Falck,[‡] and Lanny S. Liebeskind*,[†]

Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, United States, and Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390, United States

chemLL1@emory.edu

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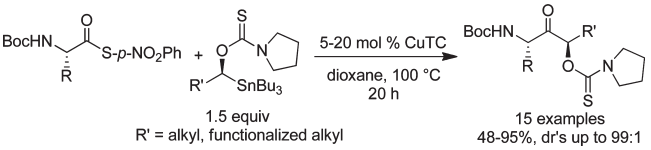
ABSTRACT



A stereocontrolled synthesis of α-amino-α′-alkoxy ketones is described. This pH-neutral copper(I) thiophene-2-carboxylate (CuTC)-catalyzed cross-coupling of amino acid thiol esters and chiral nonracemic α-alkoxyalkylstannanes gives α-amino-α′-alkoxy ketones in good to excellent yields with complete retention of configuration at the α-amino- and α-alkoxy-substituted stereocenters.

Enantioenriched α-alkoxy ketones are common moieties found in natural products and biologically active compounds. They are also useful building blocks in organic synthesis.[1] The construction of enantioenriched α-alkoxy ketones is known,[2] with recent studies[3] focusing on asymmetric benzoin condensations[4] and the asymmetric α-hydroxylation of ketones[5] or tin enolates[6] using chiral nonracemic catalysts. Complementary synthetic approaches to α-alkoxy ketones were developed in which the sp^3 carbon of an α-alkoxyalkylstannane is transferred to an acyl chloride *via* Stille-type cross-couplings using either Pd/Cu cocatalysts[7] or Cu-only catalysts.[7c,8] These reactions proceed with ca. 98% retention of stereochemistry at the α-carbon center of enantioenriched α-alkoxyalkylstannanes.[7b,c]

[†] Emory University.
[‡] University of Texas Southwestern Medical Center.

(1) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.

(2) (a) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, *62*, 1–365. (b) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92* 919–934.

(3) (a) Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995–2997. (b) Plietker, B. *Tetrahedron: Asymmetry* **2005**, *16*, 3453–3459.

(4) (a) Linghu, X.; Potnick, J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *126*, 3070–3071. (b) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc.* **2002**, *124*, 12084–12085. (c) Demir, A. S.; Şeşenoglu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P.; Müller, M. *Adv. Synth. Catal.* **2002**, *344*, 96–103. (d) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534–541.

(5) (a) Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112. (b) Sundén, H.; Engqvist, M.; Casas, J.; Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 6532–6535. (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1114. (d) Engqvist, M.; Casas, J.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2053–2057.

(6) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039.

(7) (a) Belosludtsev, Y. Y.; Bhatta, R. K.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5881–5882. (b) Ye, J. H.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1–5. (c) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973–5982. (d) Ye, J. H.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1993**, *34*, 8007–8010. (e) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438–7439. For a related approach to stereodefined α-sulfonamido ketones, see: (f) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666–15667.

(8) (a) Linderman, R. J.; Siedlecki, J. M. *J. Org. Chem.* **1996**, *61*, 6492–6493. (b) Falck, J. R.; Barma, D. K.; Mohapatra, S.; Bandyopadhyay, A.; Reddy, K. M.; Qia, J.; Campbell, W. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4987–4990. (c) Lange, H.; Fröhlich, R.; Hoppe, D. *Tetrahedron* **2008**, *64*, 9123–9135.

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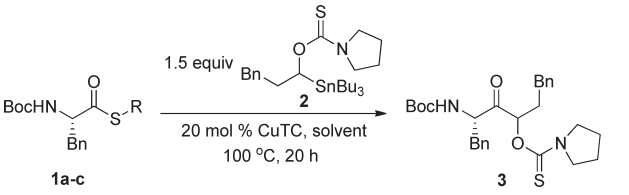
The value of the acid halide based Stille cross-coupling notwithstanding, thiol esters offer much greater functional group compatibility as cross-coupling partners compared to acid halides. They have been shown to participate in pH-neutral, Pd-catalyzed, Cu(I) carboxylate mediated couplings with a wide variety of aromatic, heteroaromatic, allylic, and alkenyl boronic acids[9] and organostannanes.[10] The Pd-catalyzed, Cu(I) carboxylate mediated reaction conditions are sufficiently mild that even racemization-sensitive peptidic thiol esters engage in efficient, racemization-free desulfitative couplings with a similar range of boron and tin reagents.[11] Peptidic ketones can also be prepared in high enantiopurity from the same substrates by two novel, Cu-only catalyzed reaction systems, one using an aerobic recycle pathway[12] and the other an anaerobic pathway that mimics the release of Cu from the metallothionein family of proteins.[13]

The pH-neutral reaction conditions of the desulfitative coupling of thiol esters with boron and tin reagents should allow the racemization-free coupling of thiol esters with transfer agents that bear stereogenic transferrable carbon centers, but no studies have yet appeared in the literature. Two indirectly relevant examples are the coupling of ethyl chlorothioformate with an α-alkoxyalkylstannane in which the C−Cl bond was selectively cleaved,[7c] and Movassaghi's stoichiometric CuTC-mediated coupling of a thiol ester with various aminomethyl stannane reagents as part of the total synthesis of the agelastatin alkaloids.[14] To address this synthetic opportunity, we describe herein the *palladium-free*, copper(I) thiophene-2-carboxylate (CuTC)-*catalyzed* desulfitative cross-coupling of α-amino acid thiol esters with Falck's enantioenriched α-alkoxyalkylstannanes[7c,15] for the straightforward stereocontrolled synthesis of α-amino-α′-alkoxy ketones.

Effective reaction parameters were determined by exploring the cross-coupling of α-amino acid thiol esters derived from L-phenylalanine with racemic pyrrolidinylthionocarbamoyl (PTC)-protected α-alkoxyalkylstannane **2**[7c] holding constant the catalyst (20 mol % CuTC) and the reaction temperature and time (100 °C for 20 h). Results are depicted in Table 1. In dioxane as solvent the isolated yield of the desired ketone increased as the electrophilicity of the L-phenylalanine thiol ester was increased from L-Boc-Phe-SEt, **1a** (entry 1, 0%), to L-Boc-Phe-SPh, **1b** (entry 2, 43%), to L-Boc-Phe-S-*p*-NO_2Ph, **1c** (entry 3, 81%). Of the different solvents screened, dioxane proved optimum, minimizing loss of the stannane **2** *via* an *O*-to-*S* rearrangement.[16] A variety of different copper sources were effective precatalysts (CuTC, CuCl, CuOAc, CuI, CuCN, $Cu(OAc)_2$, and $CuCl_2$). Among those precatalysts investigated CuTc produced slightly higher isolated yields of the ketone products and was chosen for subsequent studies. In the absence of a copper catalyst no ketone product was formed; both the thiol ester and α-alkoxyalkylstannanes were recovered.

Table 1. Optimization Studies



entry	R	solvent	yield (%)[a]
1	Et (**1a**)	dioxane	0
2	Ph (**1b**)	""	43
3	*p*-NO_2Ph (**1c**)	""	81
4	""	toluene	61
5	""	1,2-dichloroethane	48
6	""	DMF	52

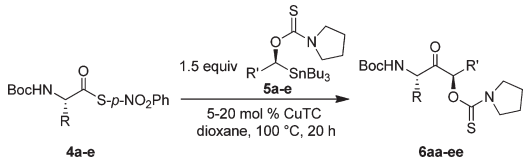
[a] Isolated yield.

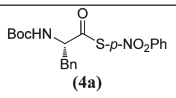
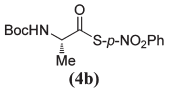
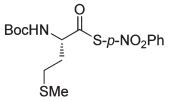
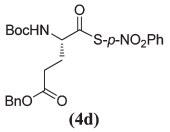
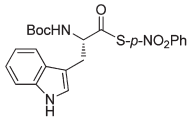
The desulfitative coupling reaction conditions used in this study are specific to the PTC-protected α-alkoxyalkylstannanes. Thus, in contrast to other desulfitative cross-couplings developed previously in our laboratory,[9,10] neither a test case sp^2-hydridized boronic acid (*p*-methoxyphenylboronic acid) nor an sp^2-hydridized organostannane (2-tri-*n*-butylstannylthiophene) participated in desulfitative coupling with thiol ester **1c** under the copper-catalyzed conditions used herein. The special effectiveness of the PTC-protected α-alkoxyalkylstannanes as reaction partners under these Cu-only reaction conditions is likely a function of the Cu-ligating ability of the PTC group.[7c] Substrate precoordination to Cu seems to play a critical role in all Cu-only catalyzed desulfitative couplings of thiol esters with boronic acids and organostannanes seen to date. Thus Cu-ligating functional groups attached to the thiol ester,[12,13,17] or to the organostannane in this current case as well as in Movassaghi's synthesis,[14] probably stabilize the *in situ* generated organocopper intermediate and/or increase the coupling reaction rate through the proximate orientation of both reaction partners around the Cu.

The scope of this desulfitative coupling of α-amino acid thiol esters and enantioenriched α-alkoxyalkylstannes was explored using the optimum reaction conditions. Results

(9) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261.
(10) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033–3035.
(11) (a) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132–1140. (b) Yang, H.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 2993–2995. (c) Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 4375–4378.
(12) Liebeskind, L. S.; Yang, H.; Li, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1417–1421.
(13) Zhang, Z.; Lindale, M. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2011**, *133*, 6403–6410.
(14) Movassaghi, M.; Siegel, D. S.; Han, S. *Chem. Sci.* **2010**, *1* 561–566.
(15) (a) He, A.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *120*, 6688–6691. (b) Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759–4762.
(16) Falck, J. R.; Patel, P. K.; Bandyopadhyay, A. *J. Am. Chem. Soc.* **2007**, *129*, 790–793. Correction: *J. Am. Chem. Soc.* **2008**, *130*, 2372.
(17) Villalobos, J. M.; Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 15734–15735.

Table 2. Thiol Ester and Enantioenriched α-Alkoxyalkylstannane Cross-Coupling



entry	thiol ester	R′	yield[a] (%)	dr[b]
1[c]	 (4a)	phenylethyl[e] (5a)	92 (6aa)	58:1
2[d]	""	cyclohexyl[f] (5b)	67 (6ab)	99:1
3[d]	""	 (5c)	57 (6ac)	-
4[d]	 (4b)	phenylethyl[e] (5a)	80 (6ba)	58:1
5[d]	""	cyclohexyl[f] (5b)	88 (6bb)	99:1
6[d]	""	 (5c)	48 (6bc)	-
7[d]	 (4c)	phenylethyl[g] (5d)	82 (6cd)	28:1
8[d]	""	cyclohexyl[f] (5b)	70 (6cb)	99:1
9[d]	 (4d)	phenylethyl[e] (5a)	73 (6da)	58:1
10[d]	""	cyclohexyl[f] (5b)	76 (6db)	99:1
11[d]	""	 (5e)	95 (6de)	-
12[c]	 (4e)	phenylethyl[e] (5a)	89 (6ea)	58:1
13[d]	""	cyclohexyl[f] (5b)	70 (6eb)	99:1
14[d]	""	 (5c)	60 (6ec)	-
15[d]	""	 (5e)	80 (6ee)	-

[a] Isolated yield. [b] dr determined by ^{1}H NMR and confirmed by HPLC chiral OJ reversed phase column using racemic mixtures derived from racemic α-alkoxystannanes as standards. [c] 5 mol % CuTC, dioxane, 100 °C, 20 h. [d] 20 mol % CuTC, dioxane, 100 °C, 20 h. [e] (*S*)-*O*-3-Phenyl-1-(tri-*n*-butylstannyl)propyl pyrrolidine-1-carbothioate (er 58:1) was used. [f] (*S*)-*O*-Cyclohexyl(tributylstannyl)methyl pyrrolidine-1-carbothioate (er 99:1) was used. [g] (*R*)-*O*-3-Phenyl-1-(tri-*n*-butylstannyl)-propyl pyrrolidine-1-carbothioate (er 28:1) was used.

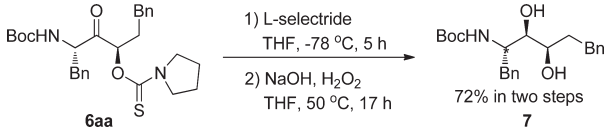
are summarized in Table 2. The enantioenriched PTC-protected stannane **5a** (er 58:1, entries 1, 4, 9, and 12) and its enantiomer **5d** (er 28:1, entry 7) participated in efficient reactions. The cyclohexyl-substituted stannane **5b** (er 99:1) also provided good yields of ketone products (entries 2, 5, 8, 10, and 13). The α,β-dialkoxystannane **5c** (entries 3, 6, and 14), which is prone to β-elimination,[15b,16] reacted smoothly with α-amino acid thiol esters to generate the corresponding trialkoxyketones in modest yields, while the more robust α-alkoxy-β-aminostannane **5e** (entries 11 and 15) produced α-alkoxy-β-amino ketones in excellent yields. Generally, a 20 mol % CuTC catalyst loading was appropriate, although a 5 mol % catalyst loading afforded the ketone products with slightly higher yields in some cases (entry 1: 92% vs 81%; entry 12: 89% vs 87%).

A variety of *N*-protected α-amino acid thiol esters derived from naturally occurring α-amino acids such as L-Phe (entries 1−3), L-Ala (entries 4−6), L-Met (entries 7 and 8), L-Glu (entries 9−11), and L-Trp (entries 12−15) also couple with α-alkoxyalkylstannes. Thus, carbamate, ester, free indole, thiol ether, and acetal functional groups were well-tolerated using this pH-neutral cross-coupling reaction.

No stereocenter epimerization was observed in the cross-couplings using the enantioenriched stannanes **5a** (er 58:1) and **5b** (er 99:1). Control experiments using racemic α-amino acid thiol esters also confirmed that no epimerization occurred at the α-amino centers.

To determine the absolute stereochemistry at the transferring stereocenter in this α-amino acid thiol ester/α-alkoxyalkylstannane coupling, Felkin−Ahn selective[18] reduction of α-amino-α′-alkoxy ketone **6aa** with L-selectride followed by deprotection of the thionocarbamate group[19] afforded the *syn*,*syn*-aminodiol **7** (Scheme 1), which matches characteristic spectroscopic data of the enantiomer of a known compound prepared by Pedersen and co-workers.[20] This result demonstrated that the cross-coupling proceeded with retention of stereochemistry at the newly formed stereocenters of the α-amino-α′-alkoxy ketones.

Scheme 1. Confirmation of Stereochemistry



A reasonable mechanistic pathway for the CuTC-catalyzed cross-coupling of α-amino acid thiol esters and

(18) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045–1056.
(19) Barma, D. K.; Bandyopadhyay, A.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4755–4757.
(20) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316–1323.
(21) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842–853. (c) Linderman, R. J.; Ghannam, A.; Badejo, I. *J. Org. Chem.* **1991**, *56*, 5213–5216. (d) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282–2316. (e) Smyj, R. P.; Chong, J. M. *Org. Lett.* **2001**, *3*, 2903–2906. (f) Monje, P.; Paleo, M. R.; Garca-Ro, L.; Sardina, F. J. *J. Org. Chem.* **2008**, *73*, 7394–7397.

enantioenriched α-alkoxyalkylstannanes is proposed in Figure 1. Similar to the known tin-to-lithium transmetalation,[21] tin-to-copper transmetalation with retention of configuration is precedented.[7c,8b,8c] In the case at hand, tin-to-copper transmetalation will generate an organocopper intermediate presumed to be stabilized by coordination to the internal thionocarbamate pendant. Reaction of this putative organocopper nucleophile with the electrophilic thiol ester would afford the desired enantioenriched α-amino-α′-alkoxy ketone and a copper thiolate, the latter of which typically terminates the catalytic cycle. The current reaction system is therefore of significant mechanistic interest because all prior Cu-based desulfitative coupling systems that are *catalytic* in Cu required a reaction design element that would scavenge the strongly bonding thiolate thereby liberating the Cu to reenter the catalytic cycle. The current reaction system requires only catalytic Cu and proceeds without a "second cycle" designed into the catalysis to retain an active form of Cu.[13]

This unprecedented Cu-catalyzed desulfitative coupling is undoubtedly driven by formation of the thermodynamically strong tin−sulfur bond that facilitates an *in situ* transmetalation between the catalytically unreactive Cu(I) thiolate and the *in situ* generated *n*-Bu_3SnOCO(2-thienyl) to regenerate the catalytically active CuTC and the thermodynamically stable end product, *n*-Bu_3SnSR (the Sn−S bond dissociation energy is 464 kJ mol^{-1};[22] the Cu−S bond dissociation energy is 274 kJ mol^{-1} [23]). This assumption was supported by the observed formation of Bu_3SnS-*p*-NO_2Ph in a ca. 1:1 ratio to the desired ketone products.

The overall reaction is a delicately balanced process, since the buildup of Bu_3SnS-*p*-NO_2Ph during the process also inhibits the catalyzed cross-coupling, presumably by ligating to Cu and filling available coordination sites. Thus, the rate of cross-coupling was significantly retarded upon addition of 1.2 equiv of *n*-Bu_3Sn-*p*-NO_2Ph to a reaction mixture comprised of thiol ester L-Boc-Phe-S-*p*-NO_2Ph (**1c**), stannane **2**, and 20 mol % CuTC. Under identical reaction conditions a lower ketone yield was observed in the presence of the added *n*-Bu_3SnS-*p*-NO_2Ph than in the standard process (48% vs 81%). Since control experiments demonstrated that the ketone forming step can take place at room temperature, the higher reaction temperature used here is required to overcome the inhibition and drive the reaction to completion in a reasonable time period

(22) Colin, R.; Drowart, J. *J. Chem. Phys.* **1962**, *37*, 1120–1125.
(23) Smoes, S.; Mandy, F.; Vander Auwera-Mahieu, A.; Drowart, J. *Bull. Soc. Chim. Belg.* **1972**, *81*, 45–56.

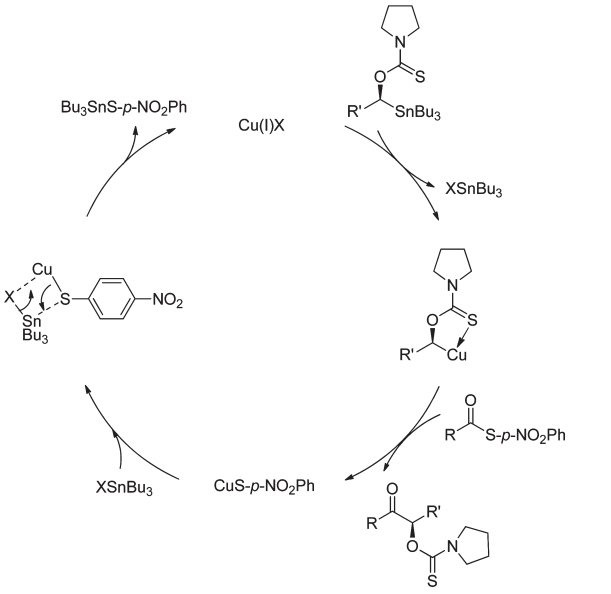


Figure 1. Proposed mechanism.

In summary, a highly efficient α-amino-α′-alkoxy ketone synthesis has been developed that proceeds *via* a copper-catalyzed transfer of secondary alkoxyalkyl groups from enantioenriched α-alkoxyalkylstannanes to α-amino acid thiol esters. This new coupling takes place with good efficiency and with complete retention of configuration at the α-carbon center of the enantioenriched α-alkoxyalkylstannanes. When coupled with stereodefined reduction of the ketone, this method provides a facile stereocontrolled construction of acyclic molecules bearing contiguous heteroatom substituted stereocenters.

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Supporting Information Available. Experimental procedures, synthesis, and characterization of all new compounds and scanned spectra. This material is available free of charge via the Internet at http://pubs.acs.org.