Synthetic Methods

DOI: 10.1002/ange.200804524

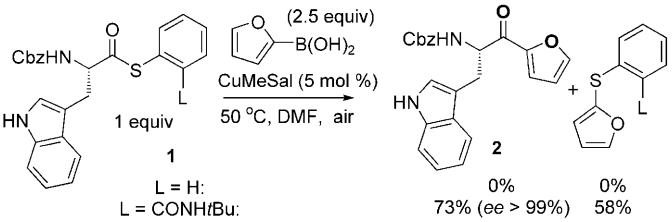
A Copper-Catalyzed, pH-Neutral Construction of High-Enantiopurity Peptidyl Ketones from Peptidic *S*-Acylthiosalicylamides in Air at Room Temperature**

Lanny S. Liebeskind, Hao Yang, and Hao Li*

In the past decade great strides have been made in discovering novel methods for the metal-catalyzed construction of C–C and C–X bonds from organic halides/sulfonates/phosphonates,[1–11] and through C–H functionalization.[12–24] The majority of these metal-catalyzed coupling reactions are now carried out using mild organic transfer agents such as boronic acids, organostannanes, and organosilanes. The synthetic power and broad impact of these modern methods used for the efficient and selective generation of a variety of bond types in a vast array of target molecules are unquestioned. Yet, significant challenges remain to be addressed by synthetic scientists. One "holy grail" is the highly chemoselective, non-enzymatic formation of a C–C or C–X bond at a specific site on a functionally complex biomolecule under biologically relevant conditions (minimal or no protecting groups, ambient temperatures, compatibility with protic solvents, and pH-neutral, aerobic, or anaerobic reaction conditions).[25–42]

New discoveries that can address this challenge will be of significant value, both for the discovery and development of new therapeutics, and as diagnostic tools in chemical biology. Herein, we describe one contribution toward that goal: a copper-catalyzed transformation of peptidic thiol esters and boronic acids into peptidyl ketones,[43–60] which are important compounds in the development of molecular therapeutics.[44,61–72] This new reaction takes place at room temperature in DMF or in DMF/H_2O (2:1 v/v) in air and requires only a catalytic amount of a Cu^I/carboxylate to mediate the reaction. This aerobic transformation is highly chemoselective and occurs only at a thiol ester capable of coordinating to Cu through its S appendage. The process is hampered neither by racemization of the reactants or products, nor by the presence of disulfide bonds or of unprotected phenol, alcohol, or indole groups. This chemistry is based upon a recently disclosed "second-generation" desulfitative coupling of thiol esters and boronic acids that takes place through a mechanistically novel copper-catalyzed, aerobic desulfitative process.[73,74]

In probing the benefits of copper-catalyzed, aerobic, desulfitative coupling for the construction of peptidyl ketones, we conducted a control experiment using tryptophan-derived thiol esters which validated the importance of the nature of the S-pendant group of the thiol ester on the reactivity of the substrate (Scheme 1). At 50 °C in DMF with copper(I) 3-methylsalicylate (CuMeSal; 5 mol %), the reaction occurred only with the tryptophan-derived thiophenyl ester bearing an *ortho* CONH*t*Bu group and not with the simple thiophenyl ester.



Scheme 1. Control experiments to demonstrate the effect of the pendant group on the sulfur center. Cbz = benzyloxycarbonyl, CuMeSal = copper(I) 3-methylsalicylate, DMF = *N*,*N*-dimethylformamide.

This result clearly confirmed the requirement of a coordinating moiety on the pendant group of the thiol ester for this copper-catalyzed, aerobic reaction. As described by our research group, [73] the reaction is rendered catalytic in Cu^I under aerobic conditions through "scavenging" of the thiolate residue with a second "sacrificial" equivalent of the boronic acid. A copper-centered transmetalation/reductive elimination sequence generates a thioether, thus removing thiolate from the reaction system and thereby regenerating Cu^I, which is available for subsequent reaction with O_2 and therefore continues the catalytic cycle.

A brief study on the influence of the amide group in the *ortho* position on the reaction rate and yield of the peptidyl ketone formation was undertaken. The reaction was carried out at room temperature, and it benefited from an increase in the CuMeSal loading to 20 mol %. Four tryptophan-derived thiol esters bearing different thiosalicylamide pendant groups (NHMe, NH*i*Pr, NH*t*Bu, *N*-morpholino) were treated with 2,4-difluorophenylboronic acid (2.5 equiv) in the presence of CuMeSal (20 mol %) in DMF at room temperature in air

[*] Prof. Dr. L. S. Liebeskind, H. Li
Department of Chemistry, Emory University
1515 Dickey Drive, Atlanta, GA 30322 (USA)
Fax: (+1) 404-727-6604
E-mail: chemLL1@emory.edu
H. Yang
Abbott Laboratories, GPRD, Process R&D, R450-NCR13-323A
1401 Sheridan Road, North Chicago, IL 60064 (USA)

[**] The National Institutes of General Medical Sciences, Department of Health and Human Services supported this investigation through grant no. GM066153. Dr. Gary Allred of Synthonix provided many of the boronic acids used in our studies.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804524.

(Figure 1). Missing from the series of thiosalicylamide pendant groups is the parent, NH_2, because the handling and transformation of this compound proved unexpectedly problematic.

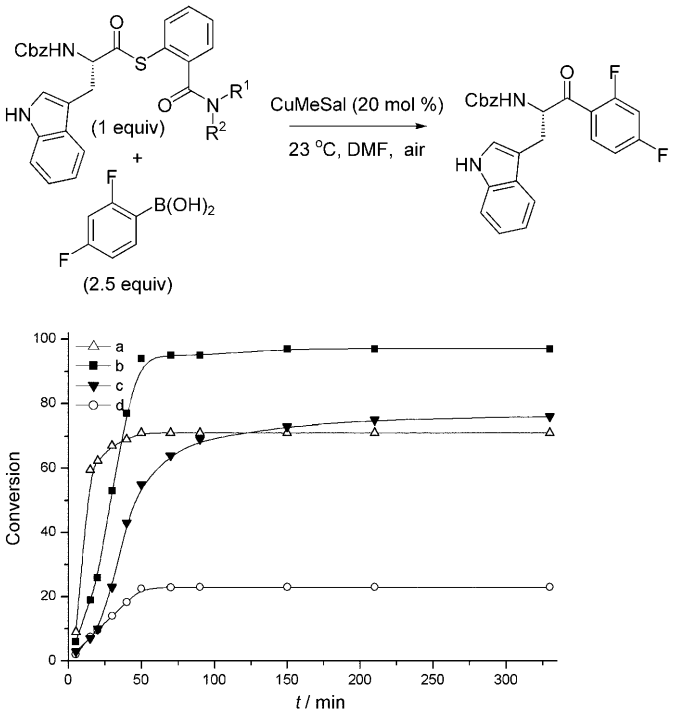
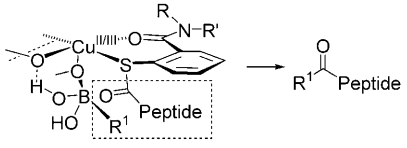


Figure 1. Influence of the thiosalicylamide substituent. In the plot a: $R^1 = H$, $R^2 = Me$; b: $R^1 = H$, $R^2 = iPr$; c: $R^1 = H$, $R^2 = tBu$; d: $R^1 - R^2 = N$-morpholino. For each thiol ester in Figure 1, two identical reactions were carried out, both containing decafluorobiphenyl as an internal standard. One reaction was used for HPLC analysis and the other to determine the yields of the isolated peptidyl ketone. Reaction time was 6 hours. No oxidative homocoupling of the boronic acid to the biphenyl was observed during the first 3 hours of the reaction. In addition to the peptidyl ketone product, these reactions also generate (2,4-$C_6H_3F_2$)S-C_6H_4(*o*-CONH*i*Pr), which is a mechanistically required side product.

Four thiosalicylamide derivatives were tested, and the initial reaction rates were inversely proportional to the steric encumbrance about the amide. The tertiary *N*-morpholino thiol ester gave the slowest initial reaction rate followed by the NH*t*Bu, NH*i*Pr, and then NHMe analogues (Figure 1). The initial rates are consistent with a reaction that proceeds through a $Cu^{II/III}$ intermediate that templates the *S*-acylthiosalicylamide and the boronic acid, such that the reactants are proximal and the thiol ester has enhanced electrophilicity (Scheme 2).[73] Diminished nonbonded steric effects make the less hindered amides better ligands for Cu, thus increasing the concentration of the copper-templated species, and accordingly providing faster rates of reaction.



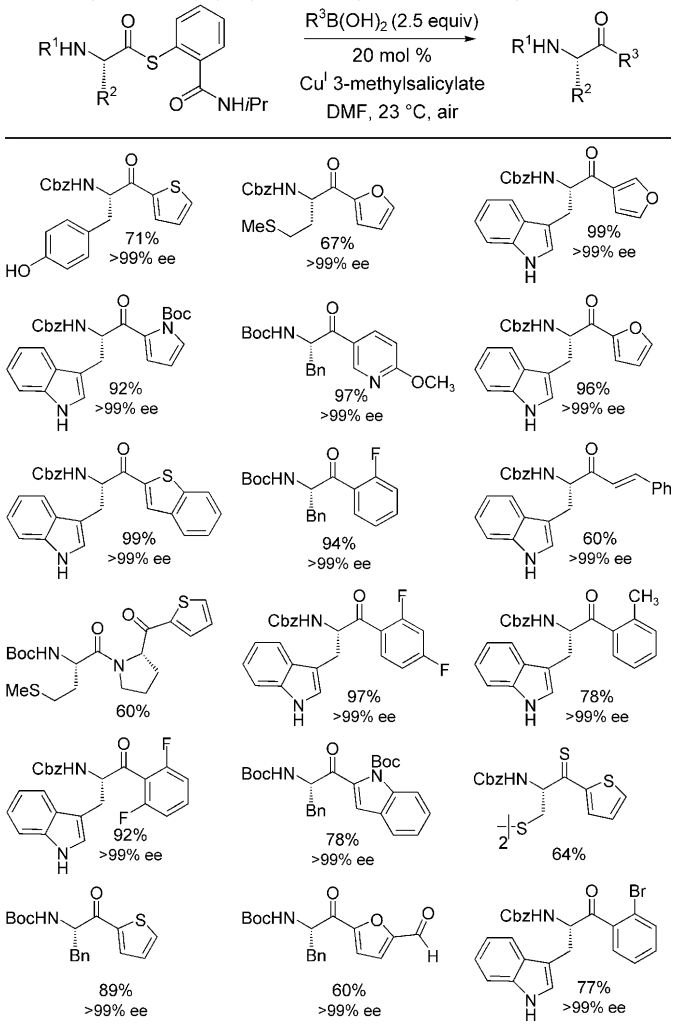
Scheme 2. The putative $Cu^{II/III}$-templated intermediate.

The reasons for the different efficiencies of the four reactions are not fully understood at this time. The reactions of both the NH*i*Pr and NH*t*Bu amide substrates showed excellent mass balances by HPLC analysis—all materials were quantitatively accounted for in the products and the unchanged starting material. In contrast, no residual starting materials were apparent in the reaction of the NHMe amide substrate, although the yield of product reached a maximum of 71%. The reaction of the *N*-morpholino amide substrate showed some residual starting material by HPLC analysis, even though the reaction stopped to give a low conversion into peptidyl ketone. Therefore, the best performing substrate was the somewhat hindered NH*i*Pr amide which reacted at a slower initial rate than the NHMe amide, but produced an excellent yield of the peptidyl ketone product within 90 minutes.

Several examples of this room-temperature, copper-catalyzed, aerobic cross-coupling reaction used for the construction of peptidyl ketones are shown in Table 1. A wide range of aryl (electron-rich or electron-deficient), heteroaryl (furyl, thienyl, benzothienyl, pyridinyl), and alkenyl boronic acids coupled efficiently with an amino acid and a dipeptide-derived thiol ester. Furthermore, sterically bulky boronic acids like 2-tolyl boronic acid and 2-*N*-Boc-pyrolyl boronic acids gave peptidyl ketones in satisfactory yields. *n*-Butyl boronic acid, the only aliphatic boronic acid examined, did not produce a peptidyl ketone upon reaction with *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*Pr). In addition to the range of boronic acids already mentioned, this reaction also tolerated thiol esters bearing metal-binding and oxidation-sensitive functional groups, such as thioether (methionine), disulfide (cystine), unprotected indole (tryptophan), and unprotected phenol (tyrosine). It can be seen from these examples that this reaction appears to be broadly useful for sensitive, highly functionalized systems. Also, the products of this aerobic desulfitative cross-coupling reaction inherit the stereochemistry of the thiol ester substrates with high fidelity. Throughout the coupling reaction and the purification process for all of the peptidyl ketones synthesized, neither racemization of the monopeptidyl ketones nor epimerization of the dipeptidyl ketone was detected.

This mild, copper-catalyzed aerobic reaction is surprisingly tolerant of the presence of water. For example, when DMF/H_2O (2:1 v/v) was used as the solvent, *N*-Boc-L-Phe-*S*-C_6H_4(*o*-CONH*i*Pr) efficiently coupled with thiophene-2-boronic acid and produced the peptidyl ketone in 70% yield (accompanied by a 73% yield of the mechanistically required thiol ether, 2-thienyl-*S*-C_6H_4(*o*-CONH*i*Pr). The compatibility of this reaction (namely, that of thiol ester *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*Pr) and 2,4-difluorophenylboronic acid) with other functional groups was probed by the addition of a stoichiometric amount of selected additives.[75] The coupling reaction was unperturbed by the addition of a primary amine (benzylamine), a secondary amine (diisopropylamine), or a tertiary amine (triethylamine). The addition of benzoic acid or of glucose did not hinder the formation of the peptidyl

Table 1: Synthesis of peptidyl ketones by aerobic Cu catalysis.[a–d]



[a] Yields of isolated products. [b] Reaction conditions: peptidyl thiol ester (1.0 equiv), boronic acid (2.5 equiv), and copper(I) 3-methylsalicylate (20 mol %) in DMF in air at room temperature for 0.5–24 hours. [c] *ee* values were determined by chiral HPLC on a reverse phase OD, AD, AS, or OJ column. In some cases the racemates were not resolved by HPLC methods and the *ee* values were not determined. [d] In addition to the peptidyl ketone product, each reaction also generated a mechanistically required thioether side product (R^3S-C_6H_4(*o*-CONH*i*Pr)) that formed from a "sacrificial" second equivalent of boronic acid and thiosalicylamide reagents. The thioether side product is removed upon chromatographic purification of the peptidyl ketone. See the Supporting Information for full experimental details. Boc = *tert*-butoxycarbonyl, Bn = benzyl.

ketone. However, the presence of salts like ammonium chloride and ammonium phosphate did inhibit the desired cross-coupling reaction, possibly by perturbation of the catalytic process through anion binding with Cu.

In conclusion, copper-catalyzed, aerobic, room-temperature reaction conditions mediate the coupling of peptidic *S*-acylthiosalicylamides with boronic acids to provide good to excellent yields of high-enantiopurity N-protected peptidyl ketones. Neither metal-binding nor oxidation-sensitive peptide residues interfere with the reaction. Further investigations of this new reaction will be focused on functionalization of the C–S bond of the protein thiol esters[76–89] at both the C terminus and the side chain. It is hoped that additional modification of the S-pendant will help in the design of easily extractable thiosalicylamide residues to facilitate simple retrieval of the peptidic ketones, and the discovery of alternative copper-catalyzed second-generation desulfitative couplings that do not require two equivalents of the boronic acid.

Experimental Section

DMF (0.1 M based on the thiol ester) was added to a mixture of *N*-Cbz-L-Trp-*S*-C_6H_4(*o*-CONH*i*Pr) (0.05 mmol, 26 mg, 1.0 equiv), 2,4-difluorophenylboronic acid (0.125 mmol, 20 mg, 2.5 equiv), copper(I) 3-methylsalicylate (0.01 mmol, 2 mg, 20 mol %). The reaction mixture was stirred in air at room temperature for 180 min and then concentrated under vacuum to remove most of the DMF (0.5 mL). The crude concentrate was then diluted with 10 volumes (5 mL) of diethyl ether. The diluted solution was washed with water and the aqueous layer was back-extracted (twice) with the same volume of diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was further purified by flash chromatography on silica gel ($CHCl_3$/EtOAc/hexanes 20:1:5) to afford the peptidyl ketone as a yellow oil (21 mg, 97 %) and the corresponding thioether (16 mg, 99 %). Peptidyl ketone data: TLC ($R_f = 0.20$, silica gel, ($CHCl_3$/EtOAc/hexanes 20:1:5)); HPLC on a chiral stationary phase using a Daicel Chirapak OD-RH column, $\lambda =$ 254 nm, flow rate: 1.0 mL min^{-1}, $T = 30$ °C, Gradient: 50 % H_2O in CH_3CN for 10 min, 75 % CH_3CN, for 12.5 min, and 100 % CH_3CN for 4.5 min, L isomer $t_R = 13.8$ min, D isomer $t_R = 12.2$ min, >99 % *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (s, 1H), 7.81 (dd, $J = 14.8$, 8.4 Hz, 1H), 7.35–7.27 (m, 7H), 7.14 (t, $J = 7.6$ Hz, 1H), 7.00 (t, $J =$ 7.6 Hz, 1H), 6.93–6.80 (m, 3H), 5.67 (d, $J = 7.6$ Hz, 1H), 5.51 (dd, $J =$ 13.2, 5.6 Hz, 1H), 5.11–5.04 (m, 2H), 3.44 (dd, $J = 15.2$, 5.6 Hz, 1H), 3.16 ppm (dd, $J = 14.8$, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 195.5, 156.0, 136.6, 136.1, 133.5, 128.7, 128.3, 127.7, 123.0, 122.3, 119.8, 118.7, 112.8, 112.6, 111.3, 109.8, 105.3, 105.1, 104.8, 67.1, 60.0, 59.9, 27.8 ppm; IR (neat): $\tilde{\nu} = 3405$ (m), 1687 (s), 1610 (s), 1502 (m), 1235 (m), 972 (m), 741 cm^{-1} (m); HRMS (FAB) calcd for $C_{25}H_{21}N_2O_3F_2$ ($[M+H]^+$): 435.1514; found: 435.1513; $[\alpha]_D^{20} +33.6$ ($c = 1.4$ g cm^{-3}, $CHCl_3$).

Received: September 14, 2008
Published online: January 14, 2009

Keywords: copper · cross-coupling · peptidomimetics · protein modifications · synthetic methods

[1] L. X. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133.
[2] N. Miyaura in *Topics in Current Chemistry*, Springer, Heidelberg, **2006**.
[3] J. F. Hartwig, *Synlett* **2006**, 1283.
[4] J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651.
[5] S. L. Buchwald, C. Mauger, G. Mignani, U. Scholzc, *Adv. Synth. Catal.* **2006**, *348*, 23.
[6] K. H. Shaughnessy, R. B. DeVasher, *Curr. Org. Chem.* **2005**, *9*, 585.
[7] R. Franzén, Y. Xu, *Can. J. Chem.* **2005**, *83*, 266.
[8] I. P. Beletskaya, *Pure Appl. Chem.* **2005**, *77*, 2021.
[9] B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599.
[10] I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337.
[11] S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

[12] R. G. Bergman, *Nature* **2007**, *446*, 391.
[13] D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.
[14] D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172.
[15] S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2008**, *130*, 3316.
[16] M. S. Chen, M. C. White, *Science* **2007**, *318*, 783.
[17] D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483.
[18] L. J. Gooßen, N. Rodriguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824.
[19] L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662.
[20] F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077.
[21] H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 1128.
[22] H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404.
[23] J. J. Mousseau, A. Larivée, A. B. Charette, *Org. Lett.* **2008**, *10*, 1641.
[24] L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276.
[25] R. A. Scheck, M. T. Dedeo, A. T. Iavarone, M. B. Francis, *J. Am. Chem. Soc.* **2008**, *130*, 11762.
[26] K. M. Marks, G. P. Nolan, *Nat. Methods* **2006**, *3*, 591.
[27] J. M. Antos, M. B. Francis, *Curr. Opin. Chem. Biol.* **2006**, *10*, 253.
[28] S. Shaunak, A. Godwin, J.-W. Choi, S. Balan, E. Pedone, D. Vijayarangam, S. Heidelberger, I. Teo, M. Zloh, S. Brocchini, *Nat. Chem. Biol.* **2006**, *2*, 312.
[29] S. Borman, *Chem. Eng. News* **2006**, *84*, 31.
[30] A. Dantas de Araújo, J. M. Palomo, J. Cramer, O. Seitz, K. Alexandrov, H. Waldmann, *Chem. Eur. J.* **2006**, *12*, 6095.
[31] C. Streu, E. Meggers, *Angew. Chem.* **2006**, *118*, 5773; *Angew. Chem. Int. Ed.* **2006**, *45*, 5645.
[32] N. S. Joshi, L. R. Whitaker, M. B. Francis, *J. Am. Chem. Soc.* **2004**, *126*, 15942.
[33] J. P. Tam, J. Xu, K. D. Eom, *Biopolymers* **2001**, *60*, 194.
[34] J. A. Prescher, C. R. Bertozzi, *Nat. Chem. Biol.* **2005**, *1*, 13.
[35] B. N. Cook, C. R. Bertozzi, *Bioorg. Med. Chem.* **2002**, *10*, 829.
[36] E. Saxon, C. R. Bertozzi, *Annu. Rev. Cell Dev. Biol.* **2001**, *17*, 1.
[37] J. A. Prescher, D. H. Dube, C. R. Bertozzi, *Nature* **2004**, *430*, 873.
[38] E. Saxon, C. R. Bertozzi, *Science* **2000**, *287*, 2007.
[39] M. Whiting, J. Muldoon, Y.-C. Lin, S. M. Silverman, W. Lindstrom, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharpless, J. H. Elder, V. V. Fokin, *Angew. Chem.* **2006**, *118*, 1463; *Angew. Chem. Int. Ed.* **2006**, *45*, 1435.
[40] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
[41] A. J. Link, D. A. Tirrell, *J. Am. Chem. Soc.* **2003**, *125*, 11164.
[42] K. E. Beatty, F. Xie, Q. Wang, D. A. Tirrell, *J. Am. Chem. Soc.* **2005**, *127*, 14150.
[43] The construction of enantiopure peptidyl ketones starting from naturally occurring amino acids is known. Although powerful, none of the known reactions take place under nonbasic (non-epimerizing) reaction conditions, nor are they general with respect to functional group compatibility, see: references [44–60].
[44] T. Mittag, K. L. Christensen, K. B. Lindsay, N. C. Nielsen, T. Skrydstrup, *J. Org. Chem.* **2008**, *73*, 1088.
[45] M. J. O'Donnell, M. D. Drew, R. S. Pottorf, W. L. Scott, *J. Comb. Chem.* **2000**, *2*, 172.
[46] B. Munoz, C.-Z. Giam, C.-H. Wong, *Bioorg. Med. Chem.* **1994**, *2*, 1085.
[47] T. Fukuyama, H. Tokuyama, *Aldrichimica Acta* **2004**, *37*, 87.
[48] M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531.
[49] T. Ooi, M. Takeuchi, D. Kato, Y. Uematsu, E. Tayama, D. Sakai, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 5073.
[50] A. G. Myers, T. Yoon, *Tetrahedron Lett.* **1995**, *36*, 9429.
[51] A. S. Florjancic, G. S. Sheppard, *Synthesis* **2003**, 1653.
[52] R. C. Klix, S. A. Chamberlin, A. V. Bhatia, D. A. Davis, T. K. Hayes, F. G. Rojas, R. W. Koops, *Tetrahedron Lett.* **1995**, *36*, 1791.
[53] M. R. Paleo, F. J. Sardina, *Tetrahedron Lett.* **1996**, *37*, 3403.
[54] J. Vazquez, F. Albericio, *Tetrahedron Lett.* **2002**, *43*, 7499.
[55] A. R. Katritzky, K. N. B. Le, L. Khelashvili, P. P. Mohapatra, *J. Org. Chem.* **2006**, *71*, 9861.
[56] K. Conrad, Y. Hsiao, R. Miller, *Tetrahedron Lett.* **2005**, *46*, 8587.
[57] J. Liu, N. Ikemoto, D. Petrillo, J. D. Armstrong, *Tetrahedron Lett.* **2002**, *43*, 8223.
[58] B. F. Bonini, M. Comes-Franchini, M. Fochi, G. Mazzanti, A. Ricci, G. Varchi, *Synlett* **1998**, 1013.
[59] A. K. Sharma, P. J. Hergenrother, *Org. Lett.* **2003**, *5*, 2107.
[60] Y. Zhang, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 15964.
[61] A. Timmons, M. Seierstad, R. Apodaca, M. Epperson, D. Pippel, S. Brown, L. Chang, B. Scott, M. Webb, S. R. Chaplan, J. G. Breitenbucher, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2109.
[62] B. E. Maryanoff, M. J. Costanzo, *Bioorg. Med. Chem.* **2008**, *16*, 1562.
[63] M. J. Costanzo, H. R. Almond, Jr., L. R. Hecker, M. R. Schott, S. C. Yabut, H.-C. Zhang, P. Andrade-Gordon, T. W. Corcoran, E. C. Giardino, J. A. Kauffman, J. M. Lewis, L. de Garavilla, B. J. Haertlein, B. E. Maryanoff, *J. Med. Chem.* **2005**, *48*, 1984.
[64] M. J. Costanzo, S. C. Yabut, H. R. Almond, Jr., P. Andrade-Gordon, T. W. Corcoran, L. de Garavilla, J. A. Kauffman, W. M. Abraham, R. Recacha, D. Chattopadhyay, B. E. Maryanoff, *J. Med. Chem.* **2003**, *46*, 3865.
[65] J. C. Powers, J. L. Asgian, O. D. Ekici, K. E. James, *Chem. Rev.* **2002**, *102*, 4639.
[66] D. L. Boger, H. Miyauchi, M. P. Hedrick, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1517.
[67] R. Tripathy, M. A. Ator, J. P. Mallamo, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2315.
[68] R. W. Marquis, Y. Ru, D. S. Yamashita, H.-J. Oh, J. Yen, S. K. Thompson, T. J. Carr, M. A. Levy, T. A. Tomaszek, C. F. Ijames, W. W. Smith, B. Zhao, C. A. Janson, S. S. Abdel-Meguid, K. J. D'Alessio, M. S. McQueney, D. F. Veber, *Bioorg. Med. Chem.* **1999**, *7*, 581.
[69] R. Calabretta, C. Giordano, C. Gallina, V. Morea, V. Consalvi, R. Scandurra, *Eur. J. Med. Chem.* **1995**, *30*, 931.
[70] P. S. Dragovich, R. Zhou, S. E. Webber, T. J. Prins, A. K. Kwok, K. Okano, S. A. Fuhrman, L. S. Zalman, F. C. Maldonado, E. L. Brown, J. W. I. Meador, A. K. Patick, C. E. Ford, M. A. Brothers, S. L. Binford, D. A. Matthews, R. A. Ferre, S. T. Worland, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 45.
[71] M. Eda, A. Ashimori, F. Akahoshi, T. Yoshimura, Y. Inoue, C. Fukaya, M. Nakajima, H. Fukuyama, T. Imada, N. Nakamura, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 919.
[72] B. M. Wagner, R. A. Smith, P. J. Coles, L. J. Copp, M. J. Ernest, A. Krantz, *J. Med. Chem.* **1994**, *37*, 1833.
[73] J. M. Villalobos, J. Srogl, L. S. Liebeskind, *J. Am. Chem. Soc.* **2007**, *129*, 15734.
[74] The synthesis of peptidyl ketones from thiol esters and boronic acids using palladium catalysts and stoichiometric amounts of Cu^{I}/carboxylate cofactors ("first-generation" desulfitative coupling) provides improved functional group compatibility relative to organolithium, -magnesium, and -zinc reagents. The desulfitative coupling reaction occurs at neutral pH at or near ambient temperature and has proven valuable for the synthesis of peptidyl ketones. Two new pH-neutral first-generation protocols have been disclosed, the first is through boronic acids (a) H. Yang, H. Li, R. Wittenberg, M. Egi, W. Huang, L. S. Liebeskind, *J. Am. Chem. Soc.* **2007**, *129*, 1132; b) H. Yang, L. S. Liebeskind, *Org. Lett.* **2007**, *9*, 2993) and a highly effective and general variant of that chemistry in which organostannanes rather than boronic acids are the reaction partners (c) H. Li, H. Yang, L. S. Liebeskind, *Org. Lett.* **2008**, *10*, 4375).

[75] Simple HPLC analysis was used for the control experiments probing the influence of additives. For the added amines, benzoic acid, and glucose, the HPLC traces only showed the peaks corresponding to the formation of products and full disappearance of the peaks corresponding to the thiol ester starting material.
[76] C. M. Gross, D. Lelievre, C. K. Woodward, G. Barany, *J. Pept. Res.* **2005**, *65*, 395.
[77] J. Alsina, S. A. Kates, G. Barany, F. Albericio, *Methods Mol. Biol.* **2005**, *298*, 195.
[78] J. Alsina, F. Albericio, *Biopolymers* **2003**, *71*, 454.
[79] J. A. Camarero, A. Adeva, T. W. Muir, *Lett. Pept. Sci.* **2000**, *7*, 17.
[80] A. Sewing, D. Hilvert, *Angew. Chem.* **2001**, *113*, 3503; *Angew. Chem. Int. Ed.* **2001**, *40*, 3395.
[81] J. Offer, C. N. C. Boddy, P. E. Dawson, *J. Am. Chem. Soc.* **2002**, *124*, 4642.
[82] S. Aimoto, *Biopolymers* **1999**, *51*, 247.
[83] J. P. Gogarten, A. G. Senejani, O. Zhaxybayeva, L. Olendzenski, E. Hilario, *Annu. Rev. Microbiol.* **2002**, *56*, 263.
[84] X.-Q. Liu, *Annu. Rev. Genet.* **2000**, *34*, 61.
[85] J. A. Camarero, *Protein Pept. Lett.* **2005**, *12*, 721.
[86] C. J. Noren, J. M. Wang, F. B. Perler, *Angew. Chem.* **2000**, *112*, 458; *Angew. Chem. Int. Ed.* **2000**, *39*, 450.
[87] R. David, M. P. O. Richter, A. G. Beck-Sickinger, *Eur. J. Biochem.* **2004**, *271*, 663.
[88] T. W. Muir, *Annu. Rev. Biochem.* **2003**, *72*, 249.
[89] K. Severinov, T. W. Muir, *J. Biol. Chem.* **1998**, *273*, 16205.

