ORGANIC LETTERS

2008
Vol. 10, No. 19
4375−4378

Synthesis of High Enantiopurity N-Protected α-Amino Ketones by Thiol Ester−Organostannane Cross-Coupling Using pH-Neutral Conditions

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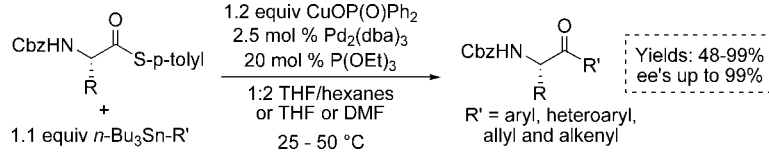
Received August 8, 2008

ABSTRACT



An efficient synthesis of high enantiopurity N-protected α-amino ketones is described. Complementing other studies using boronic acids and thiol esters, this Cu(I) diphenylphosphinate (CuDPP)-mediated, palladium-catalyzed coupling of α-amino thiol esters with aryl, heteroaryl, allyl, and alkenyl organostannanes gives N-protected α-amino ketones in high yields with high enantiopurity (in almost all cases) under mild and pH-neutral reaction conditions. The viability of π-deficient heteroarylstannanes is an advantage of this reaction compared to the related boronic acid system.

Peptidic ketones and their derived α-ketoheterocycles represent significant functionalities for the development of molecular therapeutics.[1] Potent enzyme inhibitors based on the peptidic α-ketoheterocycle motif have been found for a large number of enzymes.[1b]

Many different approaches for the synthesis of α-amino ketones and aldehydes are known, with recent studies focusing on the construction of enantiopure α-amino ketones starting from naturally occurring amino acids.[2] Among these newer protocols, the use of organozinc reagents by Fukuyama/Tokuyama[2c] and Rovis[2p] provides improved functional group compatibility relative to organolithium and organomagnesium reagents, but none of the known reactions take place under nonbasic (non-epimerizing) conditions, nor are they adequately functional group selective to be broadly general.

In contrast to the use of RLi, RMgX, and RZnX-based protocols, the metal-catalyzed reaction of COOH-equivalent functionalities with boronic acids offers the potential for a fully general and functional group compatible approach to peptidic ketone synthesis. However, known constructions of ketones by the reaction of boronic acids with various acid equivalents such as anhydrides,[3] esters,[4] acid fluorides,[2p] and acid chlorides[5] are not suitable for use with functionally complex molecules because either the carboxyl equivalent functional groups are too reactive or the reactions take place under conditions that are inappropriate for racemization sensitive substrates or products.

To address this issue, a pH-neutral, room temperature, desulfitative synthesis of peptidyl ketones from thiol esters and boronic acids using palladium catalysts and stoichiometric Cu^{I} carboxylate cofactors was recently described.[6] The reaction occurs at or near ambient temperature and has proven valuable for the synthesis of racemization sensitive peptidyl ketones.[7] As a follow-up to that first study, we describe herein a highly effective and general variant of that chemistry in which organostannanes rather than boronic acids are the reaction partners. Although organostannanes have not previously been used as reaction partners for thiol esters, vinylstannanes have been coupled with acid chlorides derived from N-protected α-amino acids.[8] Compared to the related boronic acid system, the new organostannane−peptidic thiol

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10.1021/ol8018456 CCC: $40.75
Published on Web 08/30/2008

ester coupling provides an efficient reaction using only 1.1 equiv of the stannane coupling partner, and significantly, π-deficient heteroaromatic peptidyl ketones can be prepared (which are important in drug design[1b]).

This new reaction was initially probed by exposure of the prototypical substrates L-*Z*-Phe-S-*p*-tolyl and 2-thienyl-tri-*n*-butylstannane to 2.2 equiv of the Cu(I) cofactor, copper(I) diphenylphosphinate (CuDPP),[9] in the presence of various palladium catalysts and supporting ligands. The choice of CuDPP was dictated by earlier published studies comparing copper(I) thiophene-2-carboxylate (CuTC) with CuDPP in the desulfitative coupling of thiol esters with organostannanes.[9] A brief study revealed that optimum yields of L-*Z*-Phe-2-thienyl were obtained using 2.5 mol % of $Pd_2(dba)_3$ with 20 mol % of freshly distilled $P(OEt)_3$ as the supporting ligand. The probe reactions proceeded well using THF or THF/hexanes mixtures as the reaction solvent. THF/hexanes mixtures were previously demonstrated to prevent undesired Cu-catalyzed side reactions like protodestannylation and oxidative homocoupling by minimizing the effective concentration of copper(I) carboxylate in solution.[9]

The scope and limitations of the desulfitative coupling of peptidic thiol esters and organostannanes were then explored. Results are depicted in Table 1. Freshly distilled $P(OEt)_3$ is essential for an efficient coupling, in which case a near stoichiometric quantity of CuDPP (1.2 equiv) is sufficient for most reactions, although 2.2 equiv of CuDPP delivered incrementally higher yields in some cases (entry 1: 98% vs 93%; entry 17: 80% vs 70%; entry 20: 92% vs 86%; entry 27: 84% vs 80%). Electron-rich heteroarylstannanes reacted efficiently in 1:2 THF/hexanes at or slightly above room temperature (entries 1−4, 15, 17−20, 22, 24−30). Vinyl (entry 5), allyl (entry 6), and *Z*-1-propenyl (entry 14) stannanes reacted to give acceptable to good yields of corresponding peptidyl ketone products, the latter stannane with complete retention of the double bond stereochemistry. A variety of arylstannanes (entries 7−10, 13, 23) reacted well in the cross-coupling, although a solvent switch to DMF at 50 °C was required for acceptable reaction rates and product yields in five of the six entries.

The results in Table 1 demonstrate that a diverse range of amino acid thiol esters can couple efficiently with organostannanes. Those reactants derived from nonpolar N-protected amino acids included Phe, Leu, Pro, Trp, and Met (entries 1−21). Polar N-protected amino acids studied included Ser, Tyr, Gln, His, Glu, Lys, and Arg (entries 22−29). Unprotected indole (entries 18 and 19), thioether (entries 20 and 21), alcohol (entry 22), phenol (entry 24), and amide (entry 25) functional groups were well-tolerated using this pH-neutral reaction. In addition, protected imidazole, carboxylic acid, amine, and guanidine functional groups did not interfere in the transformation (entries 26−29). Although disulfides are known to be cleaved by CuI and couple with boronic acids to produce thioethers,[10] the bisthiol ester derived from N-protected cystine reacted with 2-thienyl-tri-*n*-butylstannane to cleanly give the bisketonic product without cleaving the disulfide bond (entry 30). Given the chemical sensitivity of the disulfide linkage, this example shows the high chemoselectivity of the cross-coupling toward the C−S bond of thiol esters.

(1) (a) Timmons, A.; Seierstad, M.; Apodaca, R.; Epperson, M.; Pippel, D.; Brown, S.; Chang, L.; Scott, B.; Webb, M.; Chaplan, S. R.; Breitenbucher, J. G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2109–2113. (b) Maryanoff, B. E.; Costanzo, M. J. *Bioorg. Med. Chem.* **2008**, *16*, 1562–1596. (c) Costanzo, M. J.; Almond, H. R., Jr.; Hecker, L. R.; Schott, M. R.; Yabut, S. C.; Zhang, H.-C.; Andrade-Gordon, P.; Corcoran, T. W.; Giardino, E. C.; Kauffman, J. A.; Lewis, J. M.; de Garavilla, L.; Haertlein, B. J.; Maryanoff, B. E. *J. Med. Chem.* **2005**, *48*, 1984–2008. (d) Douangamath, A.; Dale, G. E.; D'Arcy, A.; Almstetter, M.; Eckl, R.; Frutos-Hoener, A.; Henkel, B.; Illgen, K.; Nerdinger, S.; Schulz, H.; MacSweeney, A.; Thormann, M.; Treml, A.; Pierau, S.; Wadman, S.; Oefner, C. *J. Med. Chem.* **2004**, *47*, 1325–1328. (e) Costanzo, M. J.; Yabut, S. C.; Almond, H. R., Jr.; Andrade-Gordon, P.; Corcoran, T. W.; de Garavilla, L.; Kauffman, J. A.; Abraham, W. M.; Recacha, R.; Chattopadhyay, D.; Maryanoff, B. E. *J. Med. Chem.* **2003**, *46*, 3865–3876. (f) Boger, D. L.; Miyauchi, H.; Hedrick, M. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1517–1520. (g) Bachand, B.; Tarazi, M.; St-Denis, Y.; Edmunds, J. J.; Winocour, P. D.; Leblond, L.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 287–290. (h) Tripathy, R.; Ator, M. A.; Mallamo, J. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2315–2319. (i) Marquis, R. W.; Ru, Y.; Yamashita, D. S.; Oh, H.-J.; Yen, J.; Thompson, S. K.; Carr, T. J.; Levy, M. A.; Tomaszek, T. A.; Ijames, C. F.; Smith, W. W.; Zhao, B.; Janson, C. A.; Abdel-Meguid, S. S.; D'Alessio, K. J.; McQueney, M. S.; Veber, D. F. *Bioorg. Med. Chem.* **1999**, *7*, 581–588. (j) Calabretta, R.; Giordano, C.; Gallina, C.; Morea, V.; Consalvi, V.; Scandurra, R. *Eur. J. Med. Chem.* **1995**, *30*, 931–941. (k) Dragovich, P. S.; Zhou, R.; Webber, S. E.; Prins, T. J.; Kwok, A. K.; Okano, K.; Fuhrman, S. A.; Zalman, L. S.; Maldonado, F. C.; Brown, E. L.; Meador, J. W. I.; Patick, A. K.; Ford, C. E.; Brothers, M. A.; Binford, S. L.; Matthews, D. A.; Ferre, R. A.; Worland, S. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 45–48. (l) Eda, M.; Ashimori, A.; Akahoshi, F.; Yoshimura, T.; Inoue, Y.; Fukaya, C.; Nakajima, M.; Fukuyama, H.; Imada, T.; Nakamura, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 919–924. (m) Wagner, B. M.; Smith, R. A.; Coles, P. J.; Copp, L. J.; Ernest, M. J.; Krantz, A. *J. Med. Chem.* **1994**, *37*, 1833–1840. (n) Mittag, T.; Christensen, K. L.; Lindsay, K. B.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 1088–1092.

(2) (a) O'Donnell, M. J.; Drew, M. D.; Pottorf, R. S.; Scott, W. L. *J. Comb. Chem* **2000**, *2*, 172–181. (b) Munoz, B.; Giam, C.-Z.; Wong, C.-H. *Bioorg. Med. Chem. Lett.* **1994**, *2*, 1085–1090. (c) Fukuyama, T.; Tokuyama, H. *Aldrichimica Acta* **2004**, *37*, 87–96. (d) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531–1546. (e) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K *J. Am. Chem. Soc.* **2005**, *127*, 5073–5083. (f) Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429–9432. (g) Florjancic, A. S.; Sheppard, G. S *Synthesis* **2003**, 1653–1656. (h) Klix, R. C.; Chamberlin, S. A.; Bhatia, A. V.; Davis, D. A.; Hayes, T. K.; Rojas, F. G.; Koops, R. W. *Tetrahedron Lett.* **1995**, *36*, 1791–1794. (i) Paleo, M. R.; Sardina, F. J. *Tetrahedron Lett.* **1996**, *37*, 3403–3406. (j) Vazquez, J.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 7499–7502. (k) Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. *J. Org. Chem.* **2006**, *71*, 9861–9864. (l) Conrad, K.; Hsiao, Y.; Miller, R. *Tetrahedron Lett.* **2005**, *46*, 8587–8589. (m) Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D. *Tetrahedron Lett.* **2002**, *43*, 8223–8226. (n) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Synlett* **1998**, 1013–1015. (o) Sharma, A. K.; Hergenrother, P. J. *Org. Lett.* **2003**, *5*, 2107–2109. (p) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964–15965.

(3) (a) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137–148. (b) Gooβen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3458–3460. (c) Gooβen, L. J.; Ghosh, K. *Chem. Commun.* **2001**, 2084–2085. (d) Lim, K.-C.; Hong, Y.-T.; Kim, S. *Synlett* **2006**, *12*, 1851–1854.

(4) (a) Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597–3599. (b) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N, *J. Org. Chem.* **2004**, *69*, 5615–5621.

(5) (a) Urawa, Y.; Ogura, K. *Tetrahedron Lett.* **2003**, *44*, 271–273. (b) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109–3112. (c) Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057–3060.

(6) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132–1140.

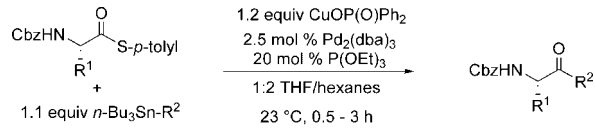
(7) Yang, H.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 2993–2995.

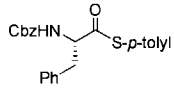
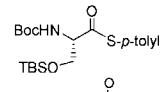
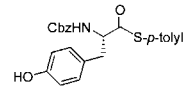
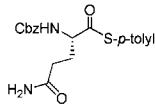
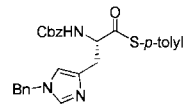
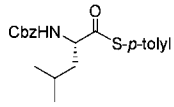
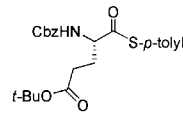
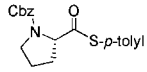
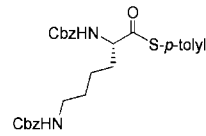
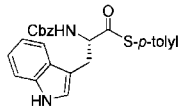
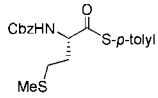
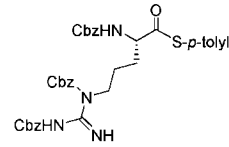
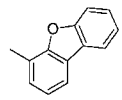
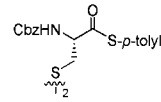
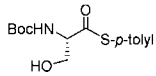
(8) (a) Bennacer, B.; Rivalle, C.; Grierson, D. S. *Eur. J. Org. Chem.* **2003**, *456*, 9–4574. (b) Crisp, G. T.; Bubner, T. P *Synth. Commun.* **1990**, *20*, 1665–1670.

(9) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033–3035.

(10) (a) Taniguchi, N. *J. Org. Chem.* **2007**, *72*, 1241–1245. (b) Taniguchi, N. *Synlett* **2006**, *9*, 1351–1354.

Table 1. Peptidyl Ketones from Thiol Esters and Organostannanes



entry	thiol ester	R^2	yield[a] (%)	ee[b] (%)	entry	thiol ester	R^2	yield[a] (%)	ee[b] (%)
1		2-thienyl	93	99	23[d]		2-methoxy-3-pyridyl	83	99
2	"	2-furyl	97	--					
3	"	2-*N*-methylpyrolyl	76	--	24		2-thienyl	68	99
4	"	2-*N*-methylindolyl	95	--					
5	"	ethenyl	52	--					
6[c]	"	2-propen-1-yl	62	99					
7[d]	"	phenyl	95	99	25[g]		2-thienyl	81	99
8[d]	"	*p*-tolyl	83	--					
9[d]	"	*p*-methoxyphenyl	82	--					
10[d]	"	*p*-chlorophenyl	98	--					
11[c]	"	2-pyridyl	72	37					
12[e]	"	3-pyridyl	89	94					
13[d]	"	1-naphthyl	91	99	26[g]		2-thienyl	78	--
14	"	*Z*-1-propenyl	81	95					
15		2-thienyl	91	99					
					27		2-thienyl	80	99
16[f]	"	2-thiazolyl	48	0					
17		2-thienyl	70	99					
					28		2-thienyl	99	99
18		2-thienyl	97	99					
19	"	*N*-methyl-2-indolyl	93	99					
20		2-thienyl	86	99					
					29		2-thienyl	65	--
21	"		79	99					
					30[h]		2-thienyl	73	--
22		2-thienyl	79	96					

[a] Isolated yield. [b] ee determined by HPLC chiral OD, OJ, or AS reversed phase column using racemic mixtures as standards. [c] 35 °C, 1:2 THF/hexanes, 2 h. [d] 50 °C, DMF, 1 h. [e] 50 °C, THF, 1 h. [f] 50 °C, 1:2 THF/hexanes, 2 h. [g] 23 °C, THF, 1 h. [h] 2-Thienyl-tri-*n*-butylstannane (2.2 equiv), $CuOP(O)Ph_2$ (2.4 equiv), $Pd_2(dba)_3$ (5 mol %), $P(OEt)_3$ (40 mol %), 23 °C, THF, 3 h.

The enantiopurity of the N-protected α-amino ketones was investigated in a number of cases. No racemization was found in most of the cases investigated. Serine, however, is known to easily racemize during peptide coupling,[11] and the serine-derived coupling system did show slight racemization. Using Boc-protected L-serine (in place of Cbz protection used for the other amino acids), the thiol ester reactant L-Boc-Ser-*S*-*p*-tolyl can be obtained in high enantiopurity after recrystallization from CH_2Cl_2/hexanes (ee >99%). However, when coupled with 2-thienyl-tri-*n*-butylstannane, a 3% ee loss was observed during silica gel chromatographic purification (entry 22). The slight racemization can be inhibited by using the O-protected variant *O*-TBS-L-Boc-Ser-*S*-*p*-tolyl; upon coupling with 2-methoxy-3-(tri-*n*-butylstannyl)pyridine, the enantiopure α-amino ketone was delivered in excellent yield after the silica gel column purification (entry 23).

For the other examples assayed for enantiopurity, only those reaction systems using π-deficient heteroarylstannanes as coupling partners showed any tendency toward racemization. Relevant examples from Table 1 are gathered for comparison in Figure 1. The peptidyl ketone products from reactions using 2-(tri-*n*-butylstannyl)thiazole and 2-(tri-*n*-butylstannyl)pyridine were obtained with significant to complete racemization. However, the racemization is not a function of the reaction conditions used; rather, it appears

(11) (a) Fenza, A. D.; Rovero, P. *Lett. Pept. Sci* **2002**, *9*, 125–129. (b) Fenza, A. D.; Tancredi, M.; Galoppini, C.; Rovero, P. *Tetrahedron Lett.* **1998**, *39*, 8529–8532.

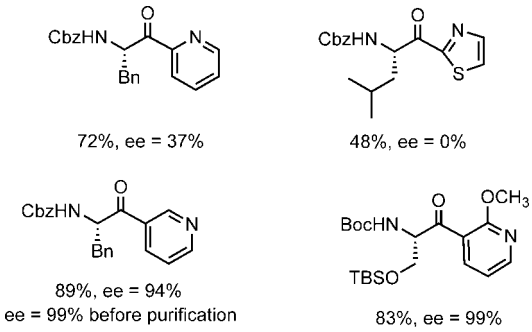


Figure 1. Structural features influencing racemization.

to be inherent to the structure of the products. A purified sample of the 2-pyridyl α-amino ketone L-Z-Phe-2-pyridyl racemized slowly in solution (24 h, ee from 37% to 31%) even in the absence of CuDPP. Not surprisingly, it is those π-deficient heteroaryl peptidyl ketones that possess functionality similar to 1,2-diketones (2-pyridyl, 2-thiazolyl) that are inherently prone to racemization, presumably via facile enol−keto equilibration. Note, in contrast, that the isomeric 3-pyridyl peptidyl ketones L-*Z*-Phe-3-pyridyl and L-*Z*-Phe-2-methoxy-3-pyridyl were significantly less prone to racemization: 3-(tri-*n*-butylstannyl)pyridine gave the desired α-amino ketone in 94% ee (crude 99% ee), while 3-(tri-*n*-butylstannyl)-2-methoxypyridine provided the peptidyl ketone in 99% ee.

In summary, a synthesis of high enantiopurity N-protected α-amino ketones has been developed using thiol esters derived from 13 amino acids and a variety of organostannanes. Structurally diverse N-protected α-amino ketones were prepared in good yields with high ee. Advantages of this new reaction compared to the related system that uses boronic acids as coupling partners[6] are the use of only 1.1 equiv of the organostannane reactant to complete the coupling reaction and the viability of π-deficient heteroarylstannanes, which are far superior to the corresponding boronic acids in overall coupling reactivity. Racemization was problematic only when some electron-deficient heteroarylstannanes were used. This mild, pH-neutral method possesses high functional group compatibility and could be very useful for constructing more complex molecular systems.

Acknowledgment. Dedicated to our new Emory colleague, Professor Huw M. L. Davies. The National Institutes of General Medical Sciences, DHHS, supported this investigation through grant No. GM066153. Dr. Gary Allred of Synthonix provided the CuDPP and many of the organostannanes used in our studies.

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.

OL8018456