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Synthesis of High Enantiopurity *N*-Protected α-Amino Ketones by Thiol Ester-Organostannane Cross-Coupling using pH-Neutral Conditions‡

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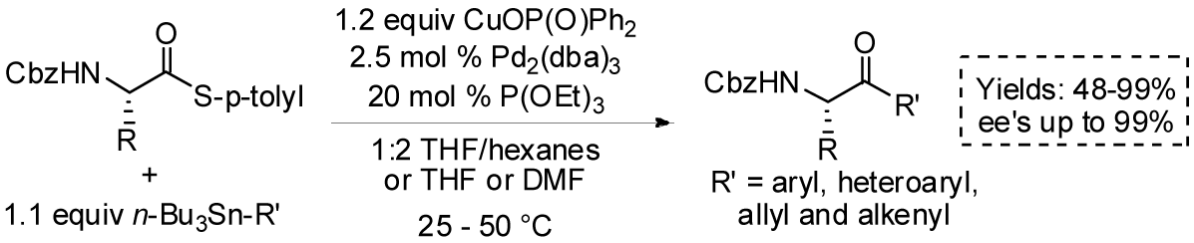
Abstract



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 takes place under non-basic (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

‡Dedicated to our new Emory colleague, Professor Huw M. L. Davies.

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Supporting Information Available Experimental procedures, synthesis and characterization of all new compounds (27 pages) and scanned spectra (89 pages). This material is available free of charge via the internet at http://pubs.acs.org

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 the carboxyl equivalent functional groups are either 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 organostannanepeptidic thiol 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 % $Pd_2(dba)_3$ 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 was 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, 21) 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 3 of the 4 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 18-19), thioether (entries 20-21), 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 bis thiol 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.

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 high enantiopurity 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 towards 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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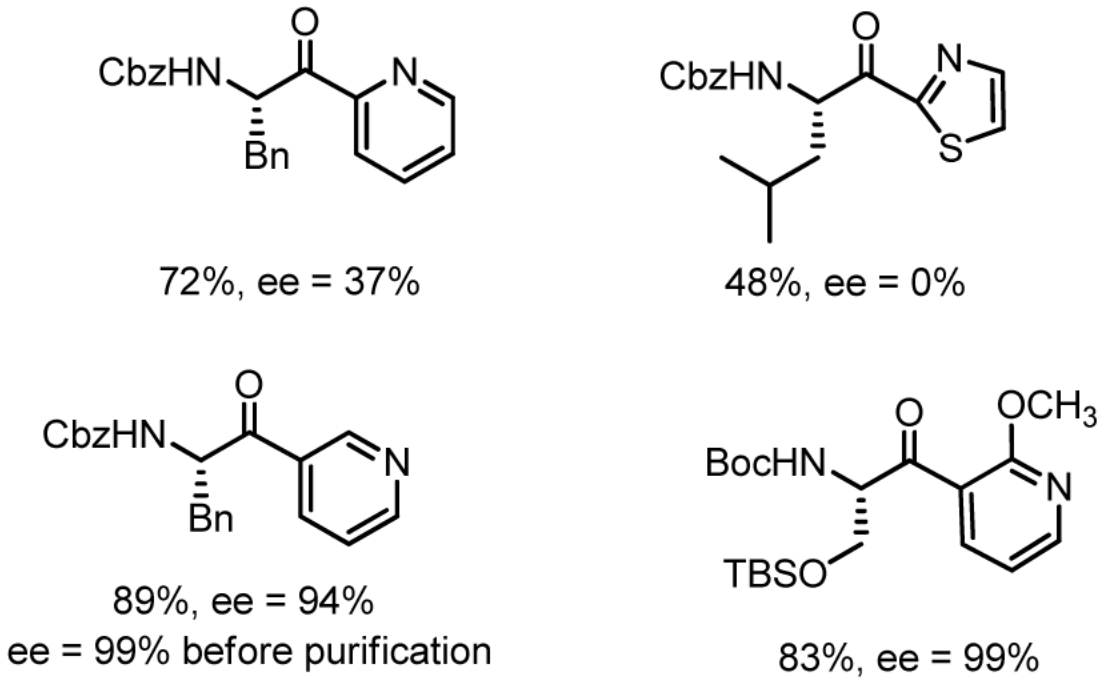
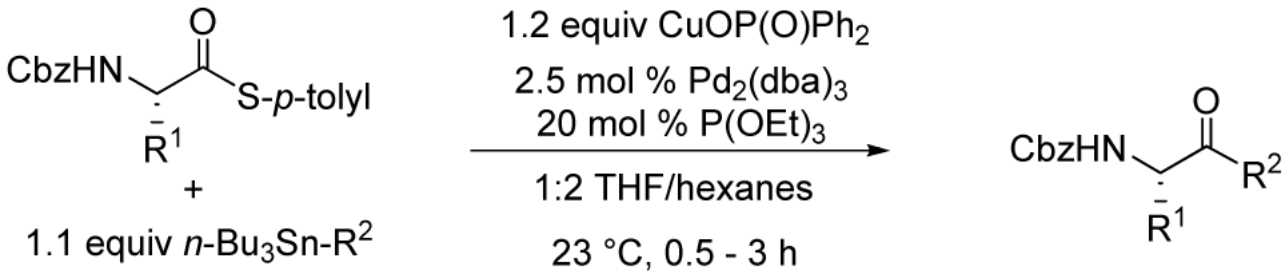
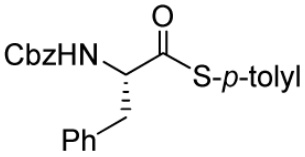
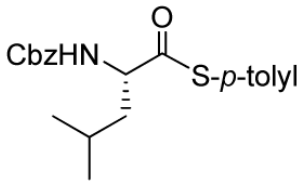
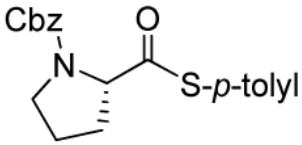


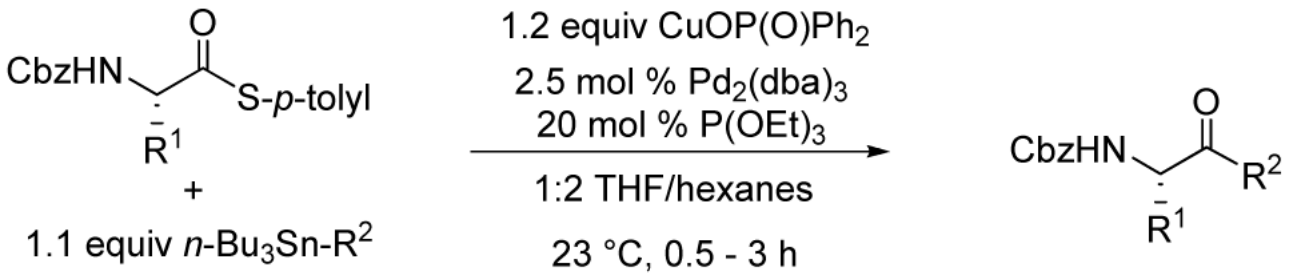
Figure 1.
Structural Features Influencing Racemization

Table 1

Peptidyl Ketones from Thiol Esters and Organostannanes



entry	thiol ester	R^2	yield[a] (%)	ee[b] (%)
1		2-thienyl	93	99
2	””	2-furyl	97	--
3	””	2-*N*-methylpyrolyl	76	--
4	””	2-*N*-methylindolyl	95	--
5	””	ethenyl	52	--
6[c]	””	2-propen-1-yl	62	99
7[d]	””	phenyl	95	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
14	””	*Z*-1-propenyl	81	95
15		2-thienyl	91	99
16[f]	””	2-thiazolyl	48	0
17		2-thienyl	70	99



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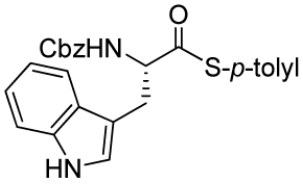
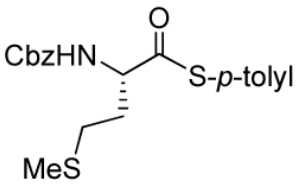
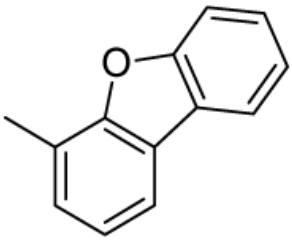
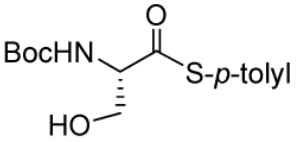
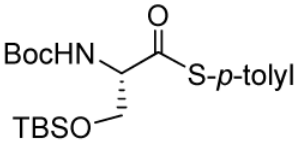
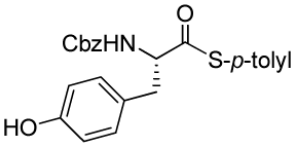
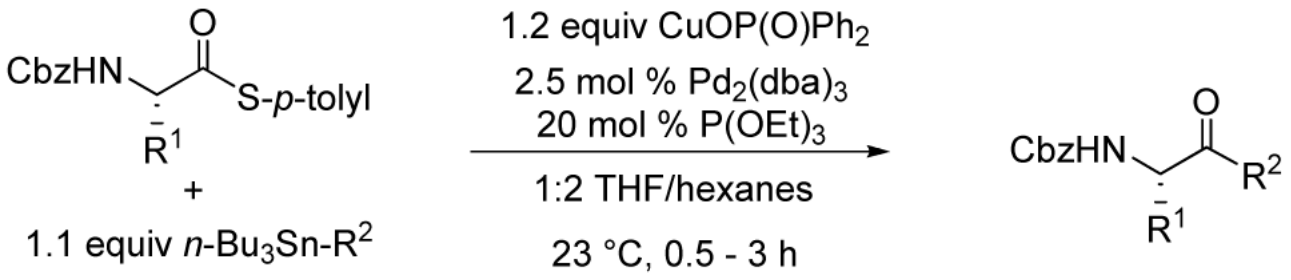
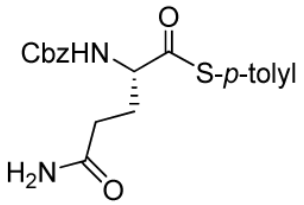
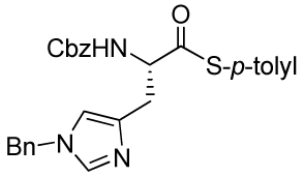
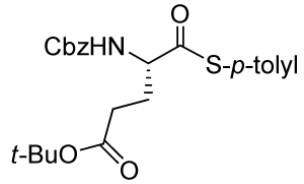
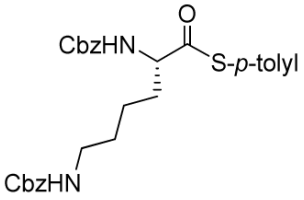
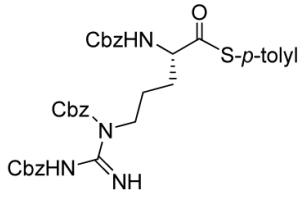
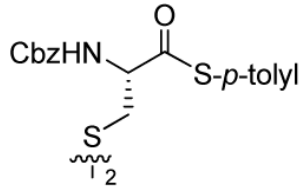
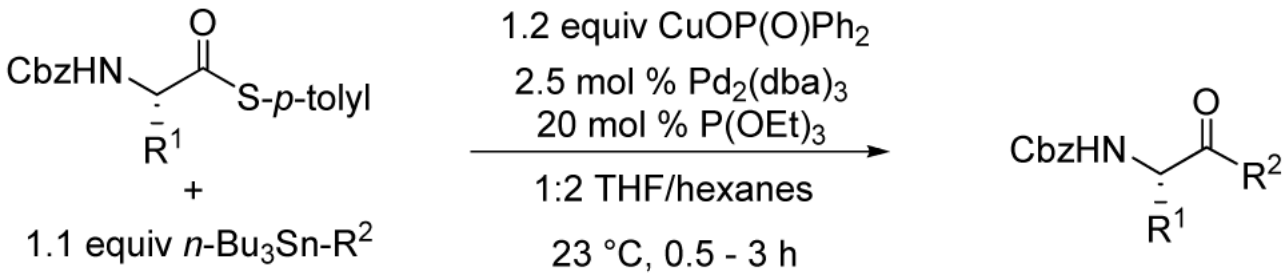
18		2-thienyl	97	99
19	””	*N*-methyl-2-indolyl	93	99
20		2-thienyl	86	99
21	””		79	99
22		2-thienyl	79	96
23[d]		2-methoxy-3-pyridyl	83	99
24		2-thienyl	68	99



entry	thiol ester	R^2	yield[a] (%)	ee[b] (%)
25[g]		2-thienyl	81	99
26[g]		2-thienyl	78	--
27		2-thienyl	80	99
28		2-thienyl	99	99
29		2-thienyl	65	--
30[h]		2-thienyl	73	--



entry	thiol ester	R^2	yield[a] (%)	ee[b] (%)

[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.