Published in final edited form as:

Org Lett. 2019 July 19; 21(14): 5762–5766. doi:10.1021/acs.orglett.9b02214.

Palladium-Catalyzed Suzuki-Miyaura Reactions of Aspartic Acid Derived Phenyl Esters

Amira H. Dardir, Nilay Hazari*, Scott J. Miller, Christopher R. Shugrue

The Department of Chemistry, Yale University, P. O. Box 208107, New Haven, Connecticut, 06520, USA

Abstract

Transition metal-catalyzed transformations of amino acids and peptides could provide a powerful method for their site-selective modification. Here, we report non-decarbonylative Pd-catalyzed Suzuki-Miyaura reactions of phenyl ester derivatives of aspartic acid to form aryl-amino ketones. These products are potentially important in the synthesis of pharmaceuticals and our methodology represents a new route to access molecules of this type.

Graphical Abstract

Peptide-based therapeutics have emerged as a complementary approach to traditional small molecule drugs, exhibiting high medicinal efficacy, selectivity, and potency, as well as low toxicity.¹ However, one reason their use in medicinal chemistry has been limited is because it is difficult to modify their pharmacokinetic properties.^{1a} In recent years there have been a number of reports describing transition metal-mediated processes to interconvert functional groups on amino acids and this has the potential to become a powerful method for peptide modification.² Changing a functional group on one or more amino acid residue can alter the properties of the peptide by enhancing in vivo stability, solubility, or membrane permeability,³ creating tags that alter photophysical characteristics, installing handles that

*Corresponding Author: nilay.hazari@yale.edu.

Supporting Information. Supporting Information containing experimental procedures and characterizing data is available free of charge at the ACS Publications website at <http://pubs.acs.org>.

The authors declare no competing financial interest.

enable additional selective functionalization,⁴ or facilitating rapid screening of derivatives to elucidate structure-activity-relationships.⁵

Transition metal-mediated processes have previously been utilized to functionalize unnatural, slightly modified, and natural amino acids (Figure 1a). For example, pseudo-halogenated tyrosine derivatives and halogenated phenylalanine derivatives can be used as the electrophile in Suzuki-Miyaura⁶ and electrocatalytic amination reactions,⁷ while organozinc reagents derived from iodoalanine, aspartic acid, or glutamic acid can be utilized as the nucleophile in Negishi reactions.⁸ Significant progress has also been made in site-selective C(sp²)-H and C(sp³)-H functionalization of natural amino acid and unnatural amino acid derivatives.⁹ Recently, arylation chemistry to form X-C(sp²) bonds (X = C, NH, O, or Se) has been developed to modify amino acids, peptides, or proteins.¹⁰ This includes natural amino acids such as cysteine,¹¹ lysine,¹² or tyrosine¹³ which can be chemoselectively modified using stoichiometric aryl Pd or Au reagents. In related work, arylated seleno-cysteine can be obtained from oxidized seleno-cysteine (Se-SR) and boronic acids using Cu reagents.¹⁴

At this stage both stoichiometric and catalytic transition metal-mediated processes that target side chain or C-terminal carboxylic acid functional groups on amino acids are rare, and they do not conserve the carbonyl moiety. For example, Ir-mediated photocatalytic couplings of carboxylic acids¹⁵ and Ni-catalyzed Negishi couplings of carboxylic acids (that have been converted into redox active esters)¹⁶ are decarboxylative processes. However, the amino ketone motif has proven to be essential for the functionality of some medicines. For instance, α -aryl-amino ketones represent a class of therapeutics employed in the clinical treatment of depression¹⁷ and nicotine dependence,¹⁸ and exhibit neuroprotective properties in mice by inhibiting the kynurenine pathway.¹⁹ Additionally, bioorthogonal reactions of ketones with hydrazines or alkoxyamines to form hydrazones or oximes, respectively, have been used as a handle for further bioconjugation, such as site-specific in vitro and cell surface protein labelling.^{4,20}

Non-decarbonylative Pd-catalyzed Suzuki-Miyaura reactions to form ketones using phenyl esters as the electrophile were recently discovered.²¹ Here, we show that this methodology can be used to catalytically modify amino acids containing carboxylic acid groups. Specifically, the esterification of carboxylic acids via a simple base-mediated process to form phenyl ester derivatives²² is followed by Pd-catalyzed non-decarbonylative cross-coupling to form ketone derivatives of aspartic acid. To the best of our knowledge, this work is the first example of a catalytic cross-coupling reaction to transform amino esters to amino ketones.

Motivated by previous work demonstrating that (η^3 -1-^tBu-indenyl)Pd(IPr)(Cl) (**1**) is an active catalyst for Suzuki-Miyaura reactions of organic phenyl esters,^{21b,21c} this precatalyst was selected for the coupling of a phenyl ester derivative of a protected aspartic acid, Boc-Asp(OPh)-O^tBu, with 4-methoxyphenylboronic acid. Our initial reactions indicated that hydrolysis of the phenyl ester to form Boc-Asp-O^tBu was a significant problem. While changing the phenyl group on the ester to electronically and sterically different aryl groups led only to comparable or lower yields, careful optimization of the reaction conditions

minimized hydrolysis (see SI). Under our optimized conditions near quantitative coupling of Boc-Asp(OPh)-O^tBu with 4 equiv. of 4-methoxyphenylboronic acid was observed using 10 mol% of **1** and 4.4 equiv. of K₂CO₃ as the base in THF at 60 °C (Table 1, Entry 1). Analysis of the product using chiral HPLC indicates that there was no racemization of the amino acid during the reaction and only a single stereoisomer of the amino ketone was formed (see SI).

Precatalyst **1** resulted in higher yields compared to other commonly used precatalysts, such as (η³-cin-namyl)Pd(IPr)(Cl) and PEPPSI-IPr (Entries 3 & 4), presumably due to the rapid activation of this system.^{21c,23} The IPr ancillary ligand is important as utilization of other common NHC ligands, such as SIPr, IMes, and IPent (Entries 5–7), resulted in a decrease in yield. Additionally, precatalysts containing several common phosphine ligands gave negligible yields (see SI). The use of K₂CO₃ as the base is crucial as other common inorganic bases, including K₃PO₄, Na₂CO₃, and Cs₂CO₃, showed minimal product formation (Entries 8–10). Small amounts of water (10 equiv.) can result in a large decrease in yield due to hydrolysis of the phenyl ester (Entry 11 & see SI). The choice of N-terminal protecting group for aspartic acid is also important. For example, when a carboxybenzyl (Cbz) protecting group is used instead of a ^tBuoxycarbonyl (Boc) group, a 73% of the cross-coupled product is observed under the standard conditions (Eq 1). Finally, the coupling of alkyl esters is significantly more difficult than the coupling of aryl esters so the protection of the C-terminus of aspartic acid as a ^tBu or Me ester prevented deleterious side reactivity at this position.²⁴

(Eq 1)

Using our optimized conditions, the scope of the boronic acid was explored (Figure 2). Substrates with electron-neutral, electron-donating, or mildly electron-withdrawing substituents on the arylboronic acid were coupled in good to high yields (**2a**, **c**, **e**, **f**). However, low yields were observed for strongly electron-withdrawing 4-trifluorophenylboronic acid (**2i**). While, 2-substituted arylboronic acids could be coupled (**2b**, **d**), 2,6-substituted substrates showed minimal formation of the product by LCMS (see SI). 3-heterarylboronic acids were coupled in good yields (**2i**, **j**), while 2-heteroaryl boronic acids, which readily undergo protodeborylation,²⁵ were challenging to couple (**2k**). For example, 2-thienylboronic acid gave low yields and 2-furylboronic acid showed no product under optimized conditions. Finally, extended aromatic boronic acids at the 1-and 2-positions showed moderate yields (**2g**, **h**). Overall, these reactions represent the first examples of non-decarbonylative Suzuki-Miyara reactions of aspartic acid derivatives and more generally a rare catalytic reaction targeting carboxylic acid side groups of amino acids. Additionally, at this stage organic amino ketones are often synthesized from carboxylic acids either via stoichiometric reactions with organolithium or Grignard reagents,

or via Friedel-Crafts chemistry,²⁶ neither of which are highly functional group tolerant. Therefore, our catalytic method may also be relevant to the synthesis of amino ketones in non-amino acid based molecules.

While high yields were obtained in coupling reactions involving the phenyl ester derivative of aspartic acid, we were unable to couple the related glutamic acid. Performing the reaction of Boc-Glu(OPh)-OMe with 4-methoxy-phenylboronic acid under the optimized conditions for the aspartic acid derivative resulted in a mixture of the desired product (6%) and a 5-membered pyroglutamic acid (91%) (Eq 2). Glutamic acid and glutamine are known to generate pyroglutamic acid in the presence of acid, base, or elevated temperatures, and this side reaction normally occurs more rapidly when the residue is at the N-terminus.²⁷

(Eq 2)

Following our work with single amino acids, we extended the methodology to dipeptides. Dipeptides with the phenyl ester derivative of aspartic acid at the C-terminus were coupled with 4 equiv. 4-methoxyphenylboronic acid, 4.4 equiv. of K₂CO₃ and 20 mol% **1** in THF at 60 °C for 16 hours. The reaction was compatible with nonpolar aliphatic (**3a-c**) and aromatic side chains (**3d**), including proline and phenylalanine. Peptides containing protected heteroatoms, such as serine(O^tBu) (**3e**), and heteroaromatics, such as tryptophan(Boc) (**3f**), were also coupled in moderate to good yields. The cross-coupling reaction was not compatible with sulfides such as methionine. However, by first performing the cross-coupling reaction on Boc-Asp(OPh)-O^tBu under standard conditions, followed by methionine coupling, dipeptide Boc-Asp(4-OMe-Ph)-Met-O^tBu was obtained in 41% overall yield (Scheme 1). Synthesis of the amino ketone monomer followed by its incorporation into peptides using standard methods represents an alternative strategy to generate peptides with new functionality.

In conclusion, we have demonstrated the first examples of a catalytic non-decarbonylative Suzuki-Miyaura cross-coupling reactions of phenyl ester derivatives of Boc protected aspartic acids to form amino ketones. The reaction is compatible with dipeptides containing alkyl, aryl, heteroaromatic, or ether side groups on the N-terminus amino acid. Our results provide proof-of-principle that a coupling reaction that works well in simple organic molecules can be translated to more complicated amino acid substrates. Further work in our laboratories will focus on making these reactions more efficient and general.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Research reported in this publication was supported by the NIHGMs under Award Number R01GM120162. We thank Dr. Fabian Menges (Yale University) for help with mass spectrometry and Brian Koronkiewicz (Yale University) for valuable discussions.

REFERENCES

1. (a) Fosgerau K; Hoffmann T Peptide Therapeutics: Current Status and Future Directions. *Drug Discov. Today* 2015, 20, 122–128; [PubMed: 25450771] (b) Henninot A; Collins JC; Nuss JM The Current State of Peptide Drug Discovery: Back to the Future? *J. Med. Chem.* 2018, 61, 1382–1414. [PubMed: 28737935]
2. (a) Willems T; Schepens W; van Vlijmen HWT; Maes BUW; Ballet S The Suzuki-Miyaura Cross-Coupling as a Versatile Tool for Peptide Diversification and Cyclization. *Catalysts* 2017, 7, 74; (b) Isidro-Llobet A; Kenworthy MN; Mukherjee S; Kopach ME; Wegner K; Gallou F; Smith AG; Roschangar F Sustainability Challenges in Peptide Synthesis and Purification: From R&D to Production. *J. Org. Chem.* 2019, 84, 4615–4628. [PubMed: 30900880]
3. Di L Strategic Approaches to Optimizing Peptide ADME Properties. *AAPS J.* 2015, 17, 134–143. [PubMed: 25366889]
4. Sletten EM; Bertozzi CR Bioorthogonal Chemistry: Fishing for Selectivity in a Sea of Functionality. *Angew. Chem. Int. Ed* 2009, 48, 6974–6998.
5. Doan N-D; Molliens M. P. d.; Letourneau M; Fournier A; Chatenet D Optimization of On-Resin Palladium-Catalyzed Sonogashira Cross-Coupling Reaction for Peptides and its Use in a Structure–Activity Relationship Study of a Class B GPCR Ligand. *Eur. J. Med. Chem.* 2015, 104, 106–114. [PubMed: 26448038]
6. (a) Shieh W-C; Carlson JA A Simple Asymmetric Synthesis of 4-arylphenylalanines via Palladium-Catalyzed Cross Coupling Reaction of Arylboronic Acids with Tyrosine Triflate. *J. Org. Chem.* 1992, 57, 379–381; (b) Burk MJ; Lee JR; Martinez JP A Versatile Tandem Catalysis Procedure for the Preparation of Novel Amino Acids and Peptides. *J. Am. Chem. Soc.* 1994, 116, 10847–10848.
7. Kawamata Y; Vantourout JC; Hickey DP; Bai P; Chen L; Hou Q; Qiao W; Barman K; Edwards MA; Garrido-Castro AF; deGruyter JN; Nakamura H; Knouse K; Qin C; Clay KJ; Bao D; Li C; Starr JT; Garcia-Irizarry C; Sach N; White HS; Neurock M; Minter SD; Baran PS Electrochemically Driven, Ni-Catalyzed Aryl Amination: Scope, Mechanism, and Applications. *J. Am. Chem. Soc.* 2019, 141, 6392–6402. [PubMed: 30905151]
8. (a) Rilatt I; Caggiano L; Jackson RFW Development and Applications of Amino Acid Derived Organometallics. *Synlett* 2005, 18, 2701–2719; (b) Oswald CL; Carrillo-Marquez T; Caggiano L; Jackson RFW Negishi Cross-Coupling Reactions of α -Amino Acid-Derived Organozinc Reagents and Aromatic Bromides. *Tetrahedron* 2008, 64, 681–687; (c) Ross AJ; Lang HL; Jackson RFW Much Improved Conditions for the Negishi Cross-Coupling of Iodoalanine Derived Zinc Reagents with Aryl Halides. *J. Org. Chem.* 2010, 75, 245–248; [PubMed: 19938812] (d) Usuki T; Yanuma H; Hayashi T; Yamada H; Suzuki N; Masuyama Y Improved Negishi Cross-Coupling Reactions of an Organozinc Reagent Derived from L-Aspartic Acid with Monohalopyridines. *J. Heterocyclic Chem.* 2014, 51, 269–273.
9. (a) Ball ZT Designing Enzyme-like Catalysts: A Rhodium(II) Metallopeptide Case Study. *Acc. Chem. Res.* 2013, 46, 560–570; [PubMed: 23210518] (b) Noisier AFM; Brimble MA C–H Functionalization in the Synthesis of Amino Acids and Peptides. *Chem. Rev.* 2014, 114, 8775–8806; [PubMed: 25144592] (c) Mondal S; Chowdhury S Recent Advances on Amino Acid Modifications via C–H Functionalization and Decarboxylative Functionalization Strategies. *Adv. Synth. Catal.* 2018, 360, 1884–1912; (d) Brandhofer T; Mancheno OG Site-Selective C–H Bond Activation/Functionalization of Alpha-Amino Acids and Peptide-Like Derivatives. *Eur. J. Org. Chem.* 2018, 6050–6067.
10. (a) Zhang C; Vinogradova EV; Spokoyny AM; Buchwald SL; Pentelute BL Arylation Chemistry for Bioconjugation. *Angew. Chem. Int. Ed* 2018, 58, 4810–4839; (b) Ohata J; Martin SC; Ball ZT Metal-Mediated Functionalization of Natural Peptides and Proteins: Panning for Bioconjugation Gold. *Angew. Chem. Int. Ed* 2018, 58, 6176–6199.

11. (a) Vinogradova EV; Zhang C; Spokoyny AM; Pentelute BL; Buchwald SL Organometallic Palladium Reagents for Cysteine Bioconjugation. *Nature* 2015, 526, 687–691; [PubMed: 26511579] (b) Rojas AJ; Zhang C; Vinogradova EV; Buchwald NH; Reilly J; Pentelute BL; Buchwald SL Divergent Unprotected Peptide Macrocyclisation by Palladium-Mediated Cysteine Arylation. *Chem. Sci* 2017, 8, 4257–4263; [PubMed: 29081961] (c) Messina MS; Stauber JM; Waddington MA; Rheingold AL; Maynard HD; Spokoyny AM Organometallic Gold (III) Reagents for Cysteine Arylation. *J. Am. Chem. Soc* 2018, 140, 7065–7069. [PubMed: 29790740]
12. Lee HG; Lautrette G; Pentelute BL; Buchwald SL Palladium-Mediated Arylation of Lysine in Unprotected Peptides. *Angew. Chem. Int. Ed* 2017, 56, 3177–3181.
13. Tilley SD; Francis MB Tyrosine-Selective Protein Alkylation Using π -Allylpalladium Complexes. *J. Am. Chem. Soc* 2006, 128, 1080–1081. [PubMed: 16433516]
14. Cohen DT; Zhang C; Pentelute BL; Buchwald SL An Umpolung Approach for the Chemoselective Arylation of Selenocysteine in Unprotected Peptides. *J. Am. Chem. Soc* 2015, 137, 9784–9787. [PubMed: 26225900]
15. Chu L; Ohta C; Zuo Z; MacMillan DWC Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of ($\pm$)-Pregabalin. *J. Am. Chem. Soc* 2014, 136, 10886–10889. [PubMed: 25032785]
16. (a) Qin T; Cornella J; Li C; Malins LR; Edwards JT; Kawamura S; Maxell BD; Eastgate MD; Baran PS A General Alkyl-Alkyl Cross-Coupling Enabled by Redox-Active Esters and Alkylzinc Reagents. *Science* 2016, 352, 801–805; [PubMed: 27103669] (b) deGruyter JN; Malins LR; Baran PS Residue-Specific Peptide Modification: A Chemist's Guide. *Biochemistry* 2017, 56, 863–873; (c) deGruyter JN; Malins LR; Wimmer L; Clay KJ; Lopez-Ogalla J; Qin T; Cornella J; Liu Z; Che G; Bao D; Stevens JM; Qiao JX; Allen MP; Poss MA; Baran PS CITU: A Peptide and Decarboxylative Coupling Reagent. *Org. Lett* 2017, 19, 6196–6199; [PubMed: 29115835] (d) Edwards JT; Merchant RR; McClymont KS; Knouse KW; Qin T; Malins LR; Vokits B; Shaw SA; Bao D-H; Wei F-L; Zhou T; Eastgate MD; Baran PS Decarboxylative Alkenylation. *Nature* 2017, 545, 213–218; [PubMed: 28424520] (e) Malins LR Peptide Modification and Cyclization via Transition-Metal Catalysis. *Curr. Opin. Chem. Biol* 2018, 46, 25–32. [PubMed: 29656180]
17. Goodnick PJ; Dominguez RA; Vane CLD; Bowden CL Bupropion Slow-Release Response in Depression: Diagnosis and Biochemistry. *Biol. Psychiatry* 1998, 44, 629–632. [PubMed: 9787888]
18. (a) Jorenby DE; Fiore MC; Smith SS; Baker TB Treating Cigarette Smoking with Smokeless Tobacco: A Flawed Recommendation. *Am. J. Med* 1998, 104, 499–500; [PubMed: 9626037] (b) Rogers DF; Barnes PJ COPD: New Developments and Therapeutic Opportunities. *Trends Pharmacol. Sci* 1999, 20, 352–354. [PubMed: 10515795]
19. Stone TW; Darlington LG Endogenous Kynurenines as Targets for Drug Discovery and Development. *Nature Rev. Drug Discov.* 2002, 1, 609–620. [PubMed: 12402501]
20. Fernandes CSM; Teixeira GDG; Iranzo O; Roque ACA In Biomedical Applications of Functionalized Nanomaterials: Concepts, Development and Clinical Translation; 1st Edition ed.; Sarmento B, das Neves J, Eds.; Elsevier: 2018, p 105–138.
21. (a) Halima TB; Zhang W; Yalaoui I; Hong X; Yang Y-F; Houk KN; Newman SG Palladium-Catalyzed Suzuki–Miyaura Coupling of Aryl Esters. *J. Am. Chem. Soc* 2017, 139, 1311–1318; [PubMed: 28001393] (b) Lei P; Meng G; Shi S; Ling Y; An J; Szostak R; Szostak M Suzuki–Miyaura Cross-Coupling of Amides and Esters at Room Temperature: Correlation with Barriers to Rotation Around C–N and C–O Bonds. *Chem. Sci* 2017, 8, 6525–6530; [PubMed: 28989678] (c) Dardir AH; Melvin PR; Davis RM; Hazari N; Beromi MM Rapidly Activating Pd-Precatalyst for Suzuki–Miyaura and Buchwald–Hartwig Couplings of Aryl Esters. *J. Org. Chem* 2018, 469–477; [PubMed: 29191023] (d) Buchspies J; Szostak M Recent Advances in Acyl Suzuki Cross-Coupling. *Catalysts* 2019, 9, 53–76.
22. Shugrue CR; Miller SJ Phosphothreonine as a Catalytic Redifue in Peptide-Mediated Asymmetric Transfer Hydrogenation of 8-Aminoquinolines. *Angew. Chem. Int. Ed* 2015, 54, 11173–11176.
23. Melvin PR; Balcells D; Hazari N; Nova A Understanding Precatalyst Activation in Cross-Coupling Reactions: Alcohol Facilitated Reduction from Pd(II) to Pd(0) in Precatalysts of the Type (η^3 -allyl)Pd(L)(Cl) and (η^3 -indenyl)Pd(L)(Cl). *ACS Catal.* 2015, 5, 5596–5606.

24. Yue H; Zhu C; Rueping M Catalytic Ester to Stannane Functional Group Interconversion via Decarbonylative Cross-Coupling of Methyl Esters. *Org. Lett* 2018, 20, 385–388. [PubMed: 29297229]
25. Kinzel T; Zhang Y; Buchwald SL A New Palladium Precatalyst Allows for the Fast Suzuki-Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids. *J. Am. Chem. Soc* 2010, 132, 14073–14075. [PubMed: 20858009]
26. (a)Buckley TF III; Rapoport H α -Amino Acids as Chiral Educts for Asymmetric Products. Amino Acylation with N-Acylamino Acids. *J. Am. Chem. Soc* 1981, 103, 6157–6163;(b)De-Luca L; Giacomelli G; Porcheddu A A Simple Preparation of Ketones. N-Protected α -Amino Ketones from α -Amino Acids. *Org. Lett* 2001, 3, 1519–1521; [PubMed: 11388856] (c)Florjancic AS; Sheppard GS A Practical Synthesis of α -Amino Ketones via Aryllithium Addition to N-Boc- α -amino Acids. *Synthesis* 2003, 11, 1653–1656.
27. (a)Tam JP; Riemen MW; Merrifield RB Mechanism of Aspartimide Formation. *Pept. Res* 1988, 1, 6–18; [PubMed: 2980781] (b)Kumar A; Bachhawat AK Pyroglutamic Acid: Throwing Light on a Lightly Studied Metabolite. *Curr. Sci* 2012, 102, 288–297.

Figure 1:

a) Previous selected transition-metal mediated reactions of amino acids and peptides. **b)** This work Pd-catalyzed Suzuki-Miyaura reactions of phenyl esters amino acids.

Figure 2:

Isolated yields of products in Suzuki-Miyaura reactions using Boc-Asp(OPh)-O^tBu.

Conditions: amino acid (0.1 mmol), boronic acid (0.4 mmol), K₂CO₃ (0.44 mmol), **1** (0.01 mmol), THF (1 mL), 60 °C, 4 h. ^aTHF (0.98 mL), H₂O (0.02 mL). Yields are the average of two runs. ^bYield from a single trial performed on a 1.0 mmol scale relative to amino acid.

Figure 3:

Isolated yields of products in Suzuki-Miyaura reactions of dipeptide phenyl ester derivatives. Conditions: dipeptide (0.1 mmol), boronic acid (0.4 mmol), K_2CO_3 (0.44 mmol), **1** (0.02 mmol), THF (1 mL). Yields are the average of two runs.

Scheme 1:

Synthesis of Boc-Asp(4-OMe-Ph)-Met-OtBu via initial cross coupling followed by standard peptide coupling.

Table 1:

Optimization of a Pd-catalyzed Suzuki-Miyaura coupling with a phenyl ester derivative of protected aspartic acid.

entry	deviation from optimized condition	yield (%) ^a
1	No change	96
2	No precatalyst	<1
3	(η^3 -cmnamyl)Pd(IPrXCl) instead of 1	65
4	PEPPSI-IPr instead of 1	69
5	SIPr instead of IPr	60
6	IMes instead of IPr	83
7	IPent instead of IPr	60
8	N_2CO_3 instead of K_2CO_3	29
9	Cs_2CO_3 instead of K_2CO_3	6
10	K_3PO_4 instead of K_2CO_3	12
11	10 equiv. of water ^b	29

Conditions: Boc-Asp(OPh)-OtBu (0.0547 mmol), 4-methoxy-boronic acid (0.219 mmol), base (0.241 mmol), precatalyst (0.0547 mmol), THF (0.5 mL).

^aYields are the average of two runs deter-mined by LCMS based on calibration curve versus 1,2,4,5-tetra-methylbenzene.

^bTotal volume (THF + H₂O) of 0.5 mL. IPr = 1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene, SIPr = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene, IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene, IPent = 1,3-bis(2,6-Di-3-pentylphenyl)imidazole-2-ylidene, PEPPSI = [1,3-Bis(2,6-Diisopropyl)imidazole-2-ylidene](3-chloropyridyl)pal-ladium(II) dichloride.