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Synthesis of unnatural amino acid derivatives via palladium-catalyzed 1,4-addition of boronic acids

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ABSTRACT

Aryl and alkenyl amino acid derivatives were synthesized by a palladium-catalyzed 1,4-addition of the corresponding boronic acids to 2-acetamidoacrylate.

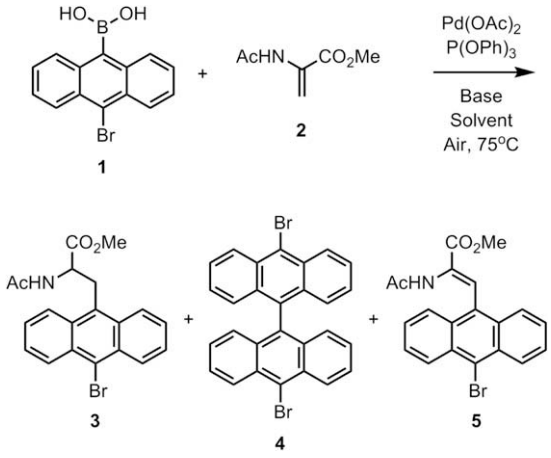
Our laboratory is interested in developing small molecule inhibitors of protein-protein interactions. Recent studies showed that the tetrapeptide pSPTF binds the carboxy terminus domains of the early onset breast cancer gene 1 (BRCT-BRCA1) with micromolar affinities.[1] Structural studies show that the phenylalanine residue (F) in pSPTF makes a key hydrophobic contact with the BRCT-BRCA1.[2] To explore this hydrophobic pocket we planned to generate unnatural amino acids with various aryl side chains.

Metal-catalyzed 1,4-addition of organometallic reagents to acetamidoacrylates is an effective strategy to access unnatural amino acids, and rhodium has been the metal of choice to carry out this transformation.[3] Recently a palladium-phosphite system was successfully used in the 1,4-addition of arylboronic acids to generate 3-arylpropanoic acid derivatives.[4] The phosphite in the palladium-catalyzed 1,4-addition suppressed the typically observed Mizoroki–Heck type of oxidative coupling product.

We speculated that palladium-phosphite-catalyzed 1,4-addition of aryl boronic acid to 2-acetamidoacrylate could provide a direct route to aryl and alkenyl side chain-containing unnatural amino acids. In this Letter, we report the synthesis of various aryl and alkenyl amino acid derivatives generated by a palladium-phosphite-catalyzed 1,4-addition of the corresponding boronic acids to acetamidoacrylate. Our studies show that palladium (low cost option) can serve as a viable alternative to rhodium for the synthesis of unnatural amino acids from acetamidoacrylates.

In the previously reported palladium-phosphite-catalyzed 1,4-addition of arylboronic acids to eneones, the formation of the desired product and two side products, namely, biaryl formed due to the oxidative homocoupling, and the Mizoroki–Heck product was reported.[4b] Our initial attempts to add a rather bulky boronic acid (10-bromoanthrace-9-ylboronic acid) to methyl-2-acetamidoacrylate using the reported palladium-phosphite-catalyzed 1,4-addition conditions failed to produce either the desired products or the side products. Therefore, we carried out a survey

Table 1
Optimization of the palladium-phosphite-catalyzed 1,4-addition of arylboronic acid to methyl-2-acetamidoacrylate



Entry[a]	Base	Solvent	% Isolated yield		
			3	**4**	**5**
1	NaOAc	DMF	0	15	20
2	CsF	DMF	25	30	0
3	Na_2CO_3	DMF	50	13	0
4	Cs_2CO_3	DMF	59	13	0
5[b]	Cs_2CO_3	DMF	0	25	40
6	Cs_2CO_3	DMSO	59	12	0
7	Cs_2CO_3	Toluene	0	9	10
8	Cs_2CO_3	THF	52	12	0
9	Cs_2CO_3	DCM	0	30	0

[a] Reaction conditions: $Pd(OAc)_2$ (0.06 mmol), $P(OPh)_3$ (0.05 mmol), **1** (1.3 mmol), and **2** (1.0 mmol).

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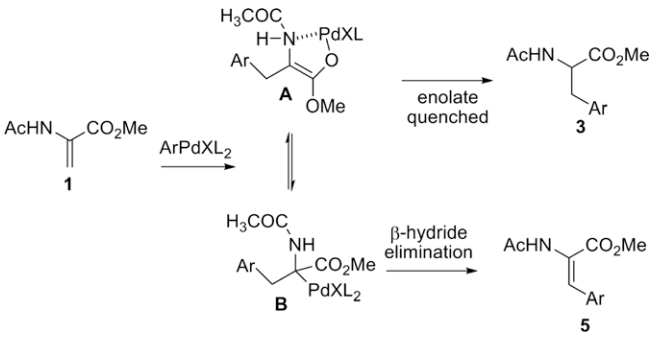


Scheme 1. Plausible mechanism.

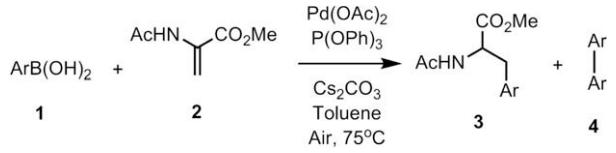
of bases and solvents to identify the optimal conditions for the reaction (summarized in Table 1).

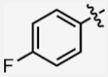
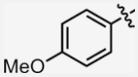
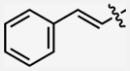
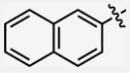
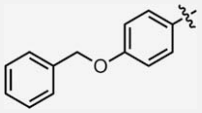
Unlike the addition to enones, we found that the use of carbonates (Table 1, entry 3 and 4) as the base yielded the highest amounts of the desired product, while the use of sodium acetate (Table 1, entry 1) resulted in the formation of the oxidative Mizoroki–Heck product. We also found that the use of polar aprotic solvents resulted in higher yields of the desired product when compared to non-polar solvents. Additionally, under catalytic conditions the reaction did not reach completion, and with stoichiometric amount of $Pd(OAc)_2$ the major product isolated was the Mizoraki–Heck product (Table 1, entry 4 vs entry 5). A plausible mechanistic pathway for this observation shown in Scheme 1 is identical to that of the corresponding addition to enones.[4] The insertion of the arylpalladium species into the acetamidoacrylate leads to two possible intermediates **A** and **B** that are probably in equillibrium.[5] The desired product is generated when the palladium enolate **A** is quenched while the β-hydride elimination of **B** will yield the Mizoroki–Heck product. The presence of excess acetate (either by the addition of sodium acetate or by the use of stoichiometric amounts of palladium acetate) drives the equilibrium toward **B** resulting in the formation of the unsaturated product **5**.

We extended this methodology (Table 1, entry 4) to generate a set of unnatural amino acids (summarized in Table 2).[6a] We obtained the desired products in modest yields (50–60%) and in most cases isolated the oxidatively homocoupled biaryl as the side product. Compounds **3a–d** and **3f** are known, while compounds **3e** and **3g** are new unnatural amino acids.[6]

In summary, we report a palladium-phosphite-catalyzed 1,4-addition of aryl or alkenyl boronic acids to generate unnatural amino acids. We are currently exploring the use of chiral phosphites in this reaction which will be reported in due course.

Table 2
Synthesis of unnatural amino acids via the palladium-phosphite-catalyzed 1,4-addition of arylboronic acid to methyl-2-acetamidoacrylate



Entry	Ar	% Yield	
		3	**4**
a		50	12
b		51	0
c		52	0
d		49	9
e		59	8
f		56	9
g		60	11

Acknowledgment

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References and notes

1. Lokesh, G. L.; Muralidhara, B. K.; Negi, S. S.; Natarajan, A. *J. Am. Chem. Soc.* **2007**, *129*, 10658–10659.
2. (a) Campbell, S. J.; Edwards, R. A.; Glover, J. N. M. *Structure* **2010**, *18*, 167–176; (b) Joseph, P. R. B.; Yuan, Z.; Kumar, E. A.; Lokesh, G. L.; Kizhake, S.; Rajarathnam, K.; Natarajan, A. *Biochem. Biophys. Res. Commun.* **2010**. doi:10.1016/j.bbrc.2010.01.098.
3. (a) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Naso, F.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 4387–4390; (b) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083–4085; (c) Chapman, C. J.; Wadsworth, K. J.; Frost, C. J. *J. Organomet. Chem.* **2003**, *680*, 206–211; (d) Navarre, L.; Darses, S.; Genet, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 719–723; (e) Navarre, L.; Martinez, R.; Genet, J. P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159–6169.
4. For review: (a) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547–4554; (b) Horiguchi, H.; Tsurugi, H.; Satoh, T.; Miura, M. *J. Org. Chem.* **2008**, *73*, 1590–1592.
5. Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817.
6. (a) *The general reaction conditions were as follows*: arylboronic acids **(1)** (1.3 mmol), methyl-2-acetamido acrylate **(2)** (1 mmol), $Pd(OAc)_2$ (0.059 mmol), $P(OPh)_3$ (0.05 mmol), and Cs_2CO_3 (1.66 mmol) were added to DMF (4 mL) and heated to 75 °C. The reaction mixture was maintained at that temperature until completion of the reaction was detected by TLC (3–5 h). The reaction was then quenched with water (5 mL) and the reaction mixture was extracted with ethyl acetate (10 mL × 3). The organic layer was washed with brine (10 mL), dried over sodium sulfate, and evaporated. The resulting crude product was purified by column chromatography using a hexane/ethyl acetate solvent system.
Methyl 2-acetamido-3-(10-bromoanthracen-9-yl)propanoate (**3**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97 (s, 3H), 3.21 (s, 3H), 4.0 (dd, 1H, *J* = 14.5, 9 Hz), 4.24 (dd, 1H, *J* = 14.5, 5.5 Hz), 5.0 (m, 1H), 6.23 (d, NH), 7.60 (m, 4H) 8.62 (d, 4H, *J* = 10 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.1, 30.9, 52.3, 53.3, 123.6, 124.3, 126.4, 126.8, 128.8, 128.9, 130.2, 131.3, 169.8, 172.3. MS(APCI$^+$): 400.2 (M+H).
(E)-Methyl-2-acetamido-5-phenylpent-4-enoate (**3e**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.56–2.71 (m, 2H), 3.68 (s, 3H), 4.66–4.72 (m, 1H), 5.92-6.00 (m, 1H), 6.10 (d, br NH), 6.38 (d, 1H, *J* = 15.62 Hz) 7.14–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.9, 23.1, 35.7, 51.9, 52.4, 123.4, 126.1, 127.6, 128.5, 134.0, 136.7, 169.7, 172.3. MS(APCI$^+$): 248.2 (M+H).
(1E, 3E)-1,4-diphenylbuta-1,3-diene (**4e**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68–6.74 (m, 4H), 6.96-7.03 (m, 4H), 7.25–7.28 (m, 4H), 7.37 (t, 8H, *J* = 7.33 Hz), 7.47 (d, 8H, *J* = 7.33 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.3, 127.5, 128.6, 129.2, 132.8, 137.3.
Methylacetylamino-(4-phenoxymethyl-phenyl)-acetate (**3g**): ^{1}H NMR (400 MHz, CD_3OD): δ 1.80 (s, 3H), 2.74–2.80 (dd, 1H, *J* = 13.67, 8.79 Hz), 2.92–2.98 (dd, 1H, *J* = 14.16, 8.30 Hz), 3.56 (s, 3H), 4.49 (dd, 1H, *J* = 8.79, 5.86 Hz), 4.93 (s, 2H), 6.80 (d, 2H, *J* = 8.79 Hz), 7.00 (d, 2H, *J* = 8.79 Hz), 7.19 (t, 1H, *J* = 7.33 Hz), 7.25 (t, 2H, *J* = 7.33 Hz), 7.31 (d, 2H, *J* = 7.33 Hz). ^{13}C NMR (100 MHz, CD_3OD): δ 21.0, 36.5, 51.5, 54.4, 69.8, 114.7, 127.4, 127.7, 128.3, 129.2, 130.0, 137.6, 158.0, 171.9, 172.5. MS(APCI$^+$): 328.2 (M+H).
4,4′-Bis-phenoxymethyl-biphenyl (**4g**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.00 (s, 4H), 6.75 (d, 4H, *J* = 6.8 Hz), 6.85 (d, 4H, *J* = 6.8 Hz), 7.32–7.43 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.9, 116.2, 116.2, 127.7, 128.1, 128.8, 128.9, 137.4, 149.8, 153.2.
(b) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409–2410; (c) Karim, A.; Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G.; Siv, C. *J. Organomet.Chem.***1986**, *317*, 93–104. (d) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Tetrahedron Lett.* **2009**, *50*, 3158.