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Synthesis of *ortho*-substituted nitroaromatics via improved Negishi coupling conditions

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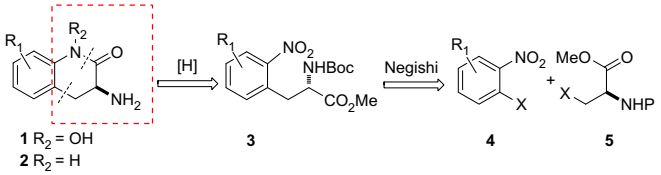
ABSTRACT

We describe modified Negishi coupling conditions that allow improved access to *ortho*-nitrophenylalanine derivatives. These useful amino acid intermediates can be further elaborated into biologically active lactams and cyclic hydroxamic acid targets.

Functionally diverse small molecules that have defined stereocenters are ubiquitous in the realm of biochemistry and drug discovery. We are particularly interested in hydroxamic acids **1**, which have recently been disclosed as potential treatments for neurological disorders[1] or bacterial infections.[2] The related carbostyril derivatives **2** have been evaluated as possible therapeutants for diseases including diabetes,[3] stroke,[4] arthritis,[5] heart disease,[6] and as analgesics.[7] Due to these potential applications, we sought to develop a general route to a key intermediate that can access both hydroxamic acid **1** and lactam **2**. Synthesis of these structures have been previously reported,[8] but herein we describe an improved and scalable sequence that utilizes a key Negishi reaction to access a broad range of functionally diverse amino ester derivatives.

Retrosynthetically, it was envisioned that Negishi coupling between a substituted *o*-nitroaromatic **4** and iodoserine derivative **5** would furnish the key phenylalanine intermediate **3** (Fig. 1), a strategy inspired by Jackson's pioneering efforts.[9] At the time these investigations were initiated, previous reports indicated that *o*-halogenated nitrobenzene derivatives coupled in low yields, typically 10–30%, and with variable reproducibility.[10] One improvement to this transformation, recently reported by the Jackson group utilized $Pd_2(dba)_3$ and SPhos to couple 2-iodonitrobenzene in 66% yield.[11] To our knowledge, this is the only example of an improved Negishi coupling on *o*-halonitrobenzenes. As the nitro group was required for subsequent transformations, we sought to optimize the Negishi conditions on these substrates and broaden the substrate scope to include additional functional handles and groups found in bioactive molecules. Herein, we describe the scope and limitations of our studies.

In the initial optimization 2-iodonitrobenzene **6** was reacted with the iodoserine derived zincate **7** generated using catalytic iodine[11,12] to provide the desired product **8** (Table 1). Coupling using conditions reported by the Jackson group[9] for 1 h provided the desired material in low yield (entry 1, 7%). Using similar conditions with lower catalyst and ligand loading, Jackson's group had reported a 28% yield of **8**. A marked improvement was observed by increasing the reaction time to 18 h (entry 2, 73%). In addition to increasing the reaction time, alternative ligands[13] were explored in combination with $Pd(OAc)_2$.[13] In the event, use of Ruphos or SPhos provided the desired product in good yields (entries 3–4, 85%). A slight improvement was found using XPhos (entry 5, 92%).[14] Furthermore, a comparable yield was obtained despite lowering the catalyst and ligand loading to 1 mol % and 2 mol %,



1 R_2 = OH
2 R_2 = H

3 4 5

Figure 1. A key Negishi coupling on *o*-nitrohalobenezene.

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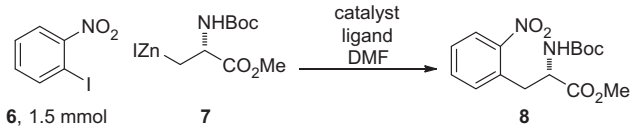
Table 1
Optimization of the Negishi coupling conditions



6, 1.5 mmol **7** **8**

Entry	Catalyst (mol %)	Ligand (mol %)	Time (h)	Equiv zincate[a]	Yield (%)[b]
1	$Pd_2(dba)_3$(5)	P(o-tol)$_3$(20)	1	1.5	7[c]
2	$Pd_2(dba)_3$(5)	P(o-tol)$_3$(20)	18	1.5	73[c]
3	$Pd(OAc)_2$(5)	RuPhos(10)	18	1.5	85
4	$Pd(OAc)_2$(5)	SPhos(10)	18	1.5	85
5	$Pd(OAc)_2$(5)	XPhos(10)	18	1.5	92
6	$Pd(OAc)_2$(1)	XPhos(2)	18	1.5	92
7	$Pd(OAc)_2$(1)	XPhos(2)	18	1.25	83
8	$Pd(OAc)_2$(1)	XPhos(2)	18	1.05	68

[a] Organozincate generated as a 1 M solution in DMF.
[b] Isolated yields after silica gel chromatography.
[c] Used TMSCl to activate the Zn to generate **7**.

respectively, (entry 6, 92%). The yield of this transformation directly correlated to the amount of zincate with higher loadings providing increased yields (compare entries 6–8). Having optimized these conditions, we sought to expand the substrate scope.

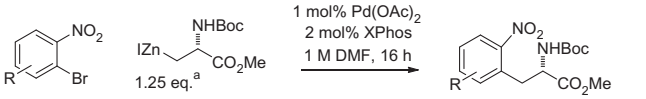
In order to broaden the substrate scope, a variety of *o*-nitrobromobenzenes were coupled using 1.25 equiv of the organozincate with 1 mol % $Pd(OAc)_2$ and 2 mol % XPhos (Table 2).[15] In addition to aryl bromides, suitably activated aryl chlorides coupled efficiently under these optimized conditions (entry 1, X = Cl, 87%; X = I, 92% yield). Consistent with the previous reports, a diverse number of functional groups were tolerated even in the presence of an activating nitro group under these conditions. For example, aldehydes, esters, and fluorides were coupled in good yields (Table 2, entries, 2–3 and 5–6) to provide useful functional group handles for further diversification. Additionally, the tolerance of fluoro groups as well as trifluoromethyl substituents allows access to pharmacologically useful final products (Table 2, entries 4–6). Even sterically hindered substrates coupled albeit in moderate yield (entry 7, 41% vs entry 1, 92%). Regioselective coupling was achieved using 2-bromo-5-chloronitrobenzene to provide the desired material in moderate yield (Table 2, entry 8, 42%).

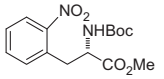
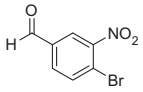
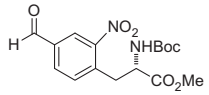
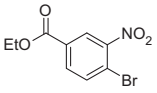
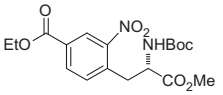
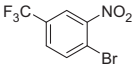
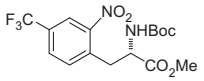
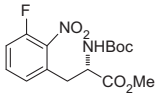
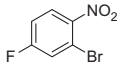
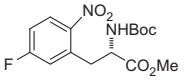
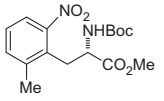
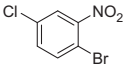
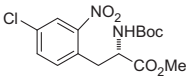
Initial forays into Negishi couplings with related nitrobromopyridines (Table 3) indicated that the coupling was less efficient than for the aryl systems as has been reported for other bromopyridines.[16] For example, 3-bromo-2-nitropyridine and 3-bromo-5-fluoro-2-nitropyridine coupled with equal efficiency (entries 1 and 3). The relative position of the nitrogen did not affect the yield in the coupling (compare entries 2 and 3). Furthermore, coupling of 6-methyl-5-fluoro-3-bromo-2-nitropyridine proceeded in a slightly improved yield (Table 3, entry 4, 29%).

Having demonstrated the scope of the improved Negishi coupling conditions, the utility and practicality of this protocol for multi-gram scale-up of hydroxamic acids **1** was assessed on a number of *o*-bromonitrobenzene targets. As a representative example, coupling of nitrobromide **8** on a 40 g scale afforded phenylalanine derivative **9** in good yield (Fig. 2, 36 g, 63% yield).[17] Subsequent reductive cyclization using 5% Pt/C under H_2 atmosphere in pyridine, followed by removal of the Boc group furnished the desired hydroxamic acid **10** in 47% yield over these two steps.[18] This scale-up sequence was effective for a broad range of substituted 2-nitrohalobenzenes.

In summary, optimized conditions have been developed for a Negishi cross coupling between an iodoserine derived zincate and a broad range of functionally diverse 2-bromonitroaromatic

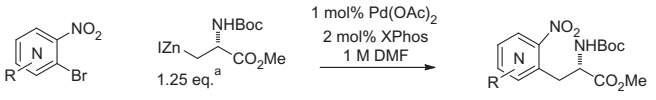
Table 2
Nitrobenzene substrate scope

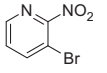
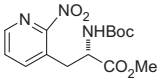
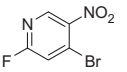
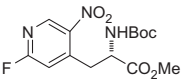
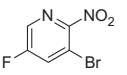
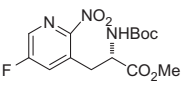
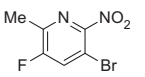
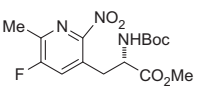


Entry	Starting material	Product	Yield[b] (%)
1			X = Cl, 87 X = I, 92
2			56
3			75
4			77
5			57
6			50
7			41
8			42

[a] Organozincate generated as a 0.1 M solution in DMF.
[b] Isolated yields.

Table 3
Bromonitropyridine substrate scope



Entry	Starting material	Product	Yield[b] (%)
1			22
2			23
3			20
4			29

[a] Organozincate generated as a 1.0 M solution in DMF.
[b] Isolated yields.

derivatives to furnish useful intermediates that provide access to biologically active small molecules. These conditions have been successfully utilized on a large scale to provide gram quantities of trifluoromethoxy phenylalanine **9**, an important intermediate

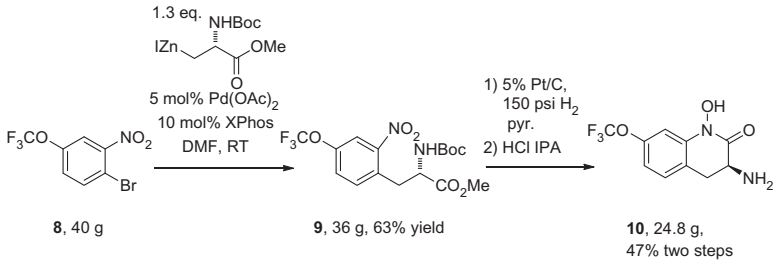


Figure 2. Utilizing the Negishi coupling as the key step in scale-up sequence.

in the synthesis hydroxamic acid derivative **10**. Future efforts will focus on optimizing this chemistry for heterocyclic substrates.

Acknowledgments

We thank Professor Gregory Fu, Robert Singer, and Martin Berliner for providing valuable insight on zinc activation methods. We thank Professors E.J. Corey, Steven Ley, and Andrew Myers for their insights into approaches for improving the pyridine coupling conditions. Finally, we are very grateful to Donn Wishka and his team of Peakdale scientists: Jessica Lyon, David Jones, Gemma Turner, Nicola Solesbury, and Paul Beagley for their scale-up efforts. Katherine Brighty is gratefully acknowledged for providing useful feedback during manuscript revisions.

References and notes

1. Claffey, M. M.; Dounay, A. B.; Gan, X.; Hayward, M. M.; Rong, S.; Tuttle, J. B.; Verhoest, P. R.. Preparation of bicyclic and tricyclic compounds as KAT II inhibitors for treating cognitive and other disorders. WO 2010146488, 2010.
2. Davis, A. L.; Hulme, K. L.; Wilson, G. T.; McCord, T. J. *Antimicrob. Agents Chemother.* **1978**, *13*, 542–544.
3. Sher, P. M.; Ellsworth, B. A. Triglyceride and triglyceride-like prodrugs of glycogenphosphorylase inhibiting compounds. US 20040142938, 2004.
4. Patankar, S. J.; Jurs, P. C. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 1053–1068.
5. Sakamoto, M.; Takasu, H.; Motoyama, M.; Kyono, K.; Oota, K. Preparation of carbostyril derivatives as extracellular matrix metal protease inhibitors. JP 08325232, 1996.
6. Kuhla, D. E.; Campbell, H. F.; Studt, W. L.; Molino, B. F. Bicyclic heteroaryl thiazole compounds and their cardiotonic uses. WO 8603749, 1986.
7. Merz, H.; Banholzer, R.; Langbein, A.; Sobotta, R.; Stockhaus, K. Preparation of 3-methylamino-3,4-dihydrocarbostyrils and analogs as analgesic agents. DE 3823576, 1990.
8. McAllister, L. A.; Bechle, B. M.; Dounay, A. B.; Evrard, E.; Gan, X.; Ghosh, S.; Kim, J.-Y.; Parikh, V. D.; Tuttle, J. B.; Verhoest, P. R. *J. Org. Chem.* **2011**, *76*, 3483–3497.
9. Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397–3404.
10. (a) Jackson, R. F. W.; Moore, R. J.; Dexter, C. S. *J. Org. Chem.* **1998**, *63*, 7875–7884; (b) Oswald, C. L.; Carrillo-Marquez, L. C.; Jackson, R. F. W. *Tetrahedron* **2008**, *64*, 681–687.
11. Concurrent to our studies reported herein, the Jackson group reported a similar approach towards improving the Negishi coupling conditions with a variety of aryl bromides: Ross, A. J.; Lang, H. L.; Jackson, R. F. W. *J. Org. Chem* **2010**, *75*, 245–248.
12. We have also used the TMSCl activation procedure reported by Jackson's group. For both methods, the organozincate solution was carefully syringed away from excess zinc in order to avoid Zn(0) mediated reduction of the nitro group to an amine.
13. For a recent review on monophosphine ligands, see: Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.
14. Xphos: (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655; Ruphos: (b) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028; SPhos: (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.
15. *General procedure:* A 1 M stock of the zincate was prepared as follows: To a suspension of zinc powder (196 mg, 2.0 equiv, based on the iodoserine, dried under vacuum using a heat gun) was added DMF (0.7 mL) and catalytic iodine (50 mg, 0.19 mmol). The reaction mixture turned from colorless to red to colorless again in ~2 min. After the return to colorless a DMF solution (1.9 mL) of the iodoserine was added followed by additional iodine (50 mg). The reaction turned from pale yellow to red, and back to colorless with an associated exotherm. The solution was stirred until the exotherm subsided, was cooled to room temp (~25 min) and was stirred until the iodoserine disappeared as monitored by TLC. The zincate solution was syringed away from the excess zinc and was added to a separate flask containing $Pd(OAc)_2$ (4 mg, 0.018 mmol), X-Phos (15 mg, 0.032 mmol), and the aryl bromide (1.88 mmol) in DMF (0.5 mL). The resulting mixture was stirred at room temperature overnight. Upon completion as indicated by TLC, the reaction was quenched with satd NH_4Cl (10 mL), poured into H_2O (50 mL) and extracted with EtOAc (2×50 mL). The organic layers were washed with H_2O (2×100 mL), brine (1×100 mL), dried over $MgSO_4$, filtered, and concentrated to a crude oil. The desired material was isolated via flash chromatography.
16. (a) Typical yields are low for Negishi couplings on pyridyl derivatives, see: Zeng, Q.; Zhang, D.; Yao, G.; Wohlhieter, G. E.; Wang, X.; Rider, J.; Reichelt, A.; Monenschein, H.; Hong, F.-T.; Falsey, J.R.; Dominguez, C.; Bourbeau, M. P.; Allen, J. G. Preparation of heterocyclic compounds as protein kinase B (PKB) modulators. WO20080716, 2009.; (b) Tabanella, S.; Valancogne, I.; Jackson, R. F. W. *Org. Biomol. Chem.* **2003**, *1*, 4254–4261; (c) Walker, M. A.; Kaplita, K. P.; Chen, T.; King, D. H. *Synlett* **1997**, *2*, 169–170.
17. Although 5 mol % $Pd(OAc)_2$ and 10 mol % XPhos were used in the Negishi coupling conditions, catalyst loadings of 1 and 2 mol %, respectively, have comparable yields on related substrates.
18. Degassed anhydrous DMF (42 mL) was added to zinc (13.72 g, 209.8 mmol) under a flow of argon. Chlorotrimethylsilane (5.30 mL, 42.0 mmol) was added and the mixture stirred vigorously for 30 min. Stirring was stopped and the zinc was allowed to settle. The supernatant was decanted under a flow of argon and the zinc washed with degassed DMF (2×20 mL). A solution of Boc-3-iodoalanine methyl ester (29.9 g, 90.9 mmol) in degassed DMF (75 mL) was added to the zinc. Upon addition an exotherm was observed. The cloudy gray solution was stirred for 30 min at room temperature and then the zinc was allowed to settle. This was repeated for a second batch of zincate. The two batches of zincate were combined by decanting the supernatant into a clean flask under a flow of argon. A solution of bromide **8** (40.0 g, 140 mmol) in degassed DMF (120 mL), palladium acetate (1.57 g, 6.99 mmol), and X-Phos (6.67 g, 14.0 mmol) were added sequentially. The reaction was heated at 40 °C. After 16 h the reaction mixture was poured into water (400 mL) and ethyl acetate (250 mL) was added. The mixture was filtered through a pad of celite, washing the filter cake with ethyl acetate (2×50 mL). The layers were separated, the aqueous extracted with ethyl acetate (100 mL) and the organics combined. The organics were then washed with brine (5×400 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting residue was purified by dry flash chromatography (2% ethyl acetate in heptane to 20%) to give compound **9** as a brown solid (35.95 g, 63%).^{1}H NMR (400 MHz, $CDCl_3$): 7.84 (s, 1H), 7.47–7.36 (m, 2H), 5.22–5.14 (m, 1H), 4.72–4.63 (m, 1H), 3.74 (s, 3H), 3.57 (dd, 1H), 3.25–3.15 (m, 1H), 1.33 (s, 9H). A mixture of compound **9** (72.18 g, 176.8 mmol) and 5% platinum on carbon (6.93 g added as a paste in water) in pyridine (360 mL) in an autoclave was charged with hydrogen (150 PSI) and stirred at rt. After 16 h, the mixture was filtered through a pad of Celite, washing with ethyl acetate (270 mL). The combined filtrate and washings were then concentrated in vacuo, azeotroped with heptane (3×180 mL), and triturated with 5% IPA in heptane (900 mL). The solids were then isolated by filtration, washing with 5% IPA in heptane (300 mL), and dried at 50 °C to give compound **10** as an off-white solid (36.7 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.46 (s, 1H), 7.23–7.17 (m, 2H), 6.93 (d 1H), 5.43–5.36 (m, 1H), 4.58–4.45 (m, 1H), 3.48–3.35 (m, 1H), 2.93–2.82 (m, 1H), 1.45 (s, 9H).LCMS (ES+): 99.53%, [M+H] = 363.1.
Compound **9** (36.7 g, 101 mmol) was stirred in 3.8 M HCl in 1,4-dioxane (395 mL) at rt for 6 h. The precipitate was isolated by filtration and slurried in diethyl ether overnight. The precipitate was again isolated by filtration washing with diethyl ether and dried in vacuo at 40 °C. Residual 1,4-dioxane was removed by heating in HPLC grade methanol at reflux for 1 h (29.59 g in 150 mL), cooling to rt and filtering to isolate the solids, then drying in vacuo at 50 °C. This was done twice–once on the bulk and once on the concentrated liquors to give in total compound **10** as a white solid (24.8 g, 82%).^{1}H NMR (400 MHz, D_2O): 7.29–7.20 (m, 2H), 6.99 (d, 1H), 4.33 (dd, 1H), 3.24 (dd, 1H), 3.17–3.06 (m, 1H). LCMS (ES+): 99.80%, [M+H] = 263.05.