Organic LETTERS

Letter

pubs.acs.org/OrgLett

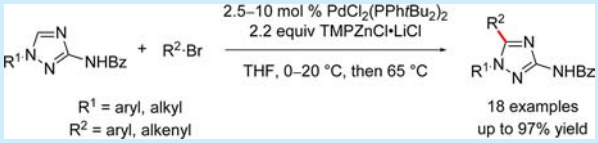
Negishi Approach to 1,5-Disubstituted 3-Amino-1*H*-1,2,4-triazoles

Jeff Shen,[†] Brian Wong,[†] Chunang Gu,[‡] and Haiming Zhang*[,†]

[†]Small Molecule Process Chemistry and [‡]Small Molecule Analytical Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States

Supporting Information

ABSTRACT: An efficient synthesis of 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles has been achieved via a Negishi coupling of aryl or vinyl bromides and 1-substituted 3-amino-1*H*-1,2,4-triazoles in the presence of Knochel's base tetramethylpiperidinylzinc chloride lithium chloride (TMPZnCl·LiCl) and catalytic bis(di-*tert*-butylphenylphosphine)palladium chloride. This chemistry tolerates a variety of electronically diverse aryl or vinyl bromides and 1-substituted 3-amino-1*H*-1,2,4-triazoles.

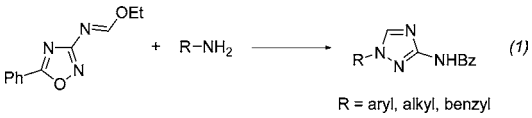


3-Amino-1*H*-1,2,4-triazoles have been paid much attention by the agrochemical and medicinal communities because of their interesting and diverse biological activities. They have been studied for potential treatment for asthma,[1] Alzheimer's disease, and Down syndrome.[2] 3-Amino-1*H*-1,2,4-triazoles have also been reported to function as inhibitors for methionine aminopeptidase-2[3] and neuropeptide Y receptor[4] as well as catalase[5] and histidine biosynthesis[6] and act as histamine H2-receptor[7] and CRF1 receptor antagonists.[8]

Various synthetic methods have been developed for 3-amino-1*H*-1,2,4-triazoles in the literature.[9] The conventional strategies for the synthesis of 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles usually involve the formation of the aminotriazole core by employing a strategically functionalized electrophile with a nitrogen containing nucleophile, for example, *N*-acylguanidine or *N*-acyl carbamimidothioate with hydrazines[10] or 1,3,4-oxadiazolium salt with cyanamide (Scheme 1).[1a,11] While a number of 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles have been synthesized by these methods, they suffered from either long synthesis or low yields or very limited scope. Therefore, a more efficient alternative is still highly desirable. Our own interest in this class of heterocycles prompted us to develop a practical synthesis of a wide variety of 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles via a cross-coupling strategy (Scheme 1).

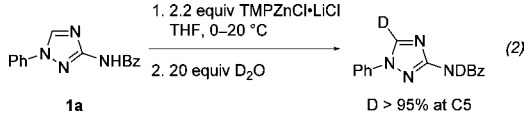
Scheme 1. Synthetic Strategies to 1,5-Disubstituted 3-Amino-1*H*-1,2,4-triazoles

We recently reported a highly efficient synthesis of 1-substituted 3-amino-1*H*-1,2,4-triazoles from ethyl *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)formimidate and anilines or amines.[12] A wide range of benzoyl-protected 1-substituted 3-aminotriazoles have thus been prepared in good to excellent yields (eq 1).



Inspired by the recent work of Knochel and co-workers,[13] we envisioned that the 5-position of these 3-amino-1*H*-1,2,4-triazoles could be metalated by tetramethylpiperidinylzinc chloride lithium chloride (TMPZnCl·LiCl, TMP = 2,2,6,6-tetramethylpiperidide) under mild conditions and the resulting zinc species could undergo Negishi coupling[14] with aryl or vinyl bromides in the presence of a palladium catalyst to generate 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles.

Our investigation commenced with the metalation of representative 3-aminotriazole **1a** using commercially available TMPZnCl·LiCl (2.2 equiv). The resulting homogeneous solution with organozinc species was then quenched with deuterium oxide (D_2O) and ^1H NMR analysis of the crude products indicated the formation of *deuterio*-**1a** with >95% D-incorporation at the 5-position (eq 2). However, only ca. 50% D-incorporation was observed when LDA was employed.



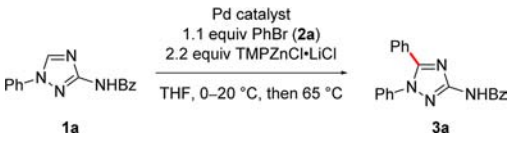
A Negishi cross-coupling reaction of the organozinc species derived from **1a** with 1.1 equiv of bromobenzene (**2a**) proceeded smoothly under mild conditions with 5 mol % of $PdCl_2(PPh_3)_2$ as catalyst in THF at 65 °C, which generated 99% conversion and

Received: July 14, 2015
Published: September 18, 2015

DOI: 10.1021/acs.orglett.5b02021
Org. Lett. 2015, 17, 4678–4681

97% assay yield in 24 h (Table 1, entry 1). Screening of the palladium catalysts including $PdCl_2$(dppf) (dppf = 1,1′-bis(diphenylphosphino)ferrocene), $PdCl_2(PCy_3)_2$ (PCy_3 = tricyclohexylphosphine), $PdCl_2$(TFP)$_2$ (TFP = trifurylphosphine),[15] $PdCl_2$(PCl-*t*-Bu$_2$)$_2$ (PXPd),[16] $PdCl_2$(Amphos)$_2$ (Amphos =4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline),[17] PEPPSI-*i*-Pr,[18] and $PdCl_2$(PPh-*t*-Bu$_2$)$_2$,[17] showed that $PdCl_2$(PPh-*t*-Bu$_2$)$_2$ was the best catalyst which afforded 99% conversion and 99% assay yield in only 2 h (Table 1, entries 2−8). Further fine-tuning the catalyst loading led to the optimal conditions which employed 2.5 mol % of $PdCl_2$(PPh-*t*-Bu$_2$)$_2$ as the catalyst in THF at 65 °C (Table 1, entries 9). Under this set of reaction conditions, the Negishi coupling using aminotriazole **1a** and bromobenzene (**2a**) afforded 99% assay yield and 94% isolated yield in 4 h. It is worth noting that the Negishi coupling reaction involving aminotriazoles and aryl or vinyl bromides was highly substrate sensitive as we observed later on during our investigation of the reaction scope and limitation. Therefore, 5 mol % catalyst loading was also frequently employed in order to obtain high reaction conversion and satisfactory yield.

Table 1. Optimization of Negishi Coupling[a]

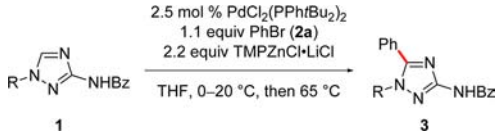


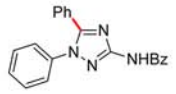
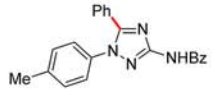
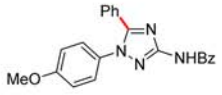
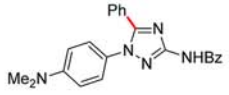
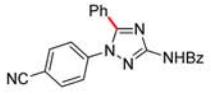
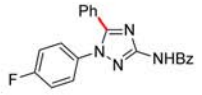
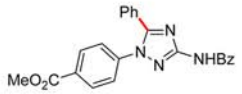
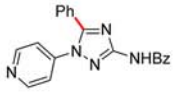
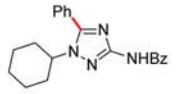
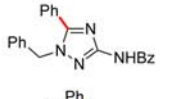
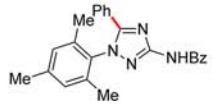
entry	catalyst	mol %	time (h)	conv[b] (%)	yield[c] (%)
1	$PdCl_2(PPh_3)_2$	5	24	99	97
2	$PdCl_2$(dppf)	5	20	99	96
3	$PdCl_2(PCy_3)_3$	5	24	71	
4	$PdCl_2$(TFP)$_2$	5	24	69	
5	$PdCl_2$(PCl-*t*-Bu$_2$)$_2$	5	24	17	
6	$PdCl_2$(Amphos)$_2$	5	3	99	100
7	PEPPSI-*i*-Pr	5	24	59	
8	$PdCl_2$(PPh-*t*-Bu$_2$)$_2$	5	2	99	99
9		2.5	4	99	99 (94)[d]
10		1	24	49	

[a]Reaction conditions: **1a** (0.26 g, 1.0 mmol), Pd catalyst (1−5 mol %), **2a** (115 μL, 1.1 equiv), TMPZnCl·LiCl (0.65 M in THF, 3.4 mL, 2.2 equiv) in THF (1.0 mL), 65 °C. [b]Determined by HPLC analysis. [c]Assay yields were obtained by quantitative HPLC analysis. [d]Isolated yield.

With a set of optimal conditions available, we then set out to investigate the scope and limitations of this Negishi coupling reaction. As shown in Table 2, a variety of 1-substituted 3-aminotriazoles underwent the Negishi coupling with bromobenzene (**2a**), smoothly generating the desired 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles.[19] Aminotriazoles substituted with an electron-neutral or electron-rich aryl group at the N1-position all produced good to excellent yields of the desired products in the presence of 2.5 mol % of catalyst (Table 2, entries 1−4). Electron-deficient substrates, for example, cyano-, fluoro-, or ester-substituted aminotriazoles **1e−g**, afforded the desired Negishi products **3e−g** in satisfactory yields, albeit requiring 5 mol % catalyst (Table 2, entries 5−7). Unfortunately, only 15% conversion was observed over 24 h when pyridine-substituted aminotriazole **1h** was subjected to the Negishi coupling conditions. The low conversion was likely caused by the low solubility of **1h** in THF as a slurry was observed throughout the reaction. In fact, when polar NMP was used as the reaction solvent, a homogeneous solution was obtained and aminotriazole **1h** readily afforded 71% yield of the desired product **3h** in 2 h (Table 2, entry 8). To our delight, cyclohexyl- and benzyl-substituted aminotriazoles **1i** and **1j** successfully generated the desired Negishi coupling products in 81% and 69% yields, respectively (Table 2, entries 9 and 10). The sterically hindered aminotriazole **1k**, however, did not afford any detectable product (Table 2, entry 11). As a control experiment, aminotriazole **1k**

Table 2. Negishi Coupling of Aminotriazoles 1 with Bromobenzene (2a)[a]



entry	triazole	product		time (h)	yield (%)[b]
1	**1a**		**3a**	4	94
2	**1b**		**3b**	2	87
3	**1c**		**3c**	3	82
4	**1d**		**3d**	3	97
5[c]	**1e**		**3e**	22	71
6[c]	**1f**		**3f**	4	77
7[c]	**1g**		**3g**	4	83
8[c,d]	**1h**		**3h**	2	71
9[c]	**1i**		**3i**	4	81
10[c]	**1j**		**3j**	3	69
11[c]	**1k**		**3k**	24	0

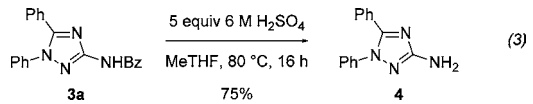
[a]Reaction conditions: **1** (1.0 mmol), $PdCl_2$(PPh-*t*-Bu$_2$)$_2$ (15.5 mg, 2.5 mol %), **2a** (115 μL, 1.1 equiv), TMPZnCl·LiCl (0.65 M in THF, 3.4 mL, 2.2 equiv) in THF (1.0 mL), 65 °C. [b]Isolated yield. [c]$PdCl_2$(PPh-*t*-Bu$_2$)$_2$ (31 mg, 5 mol %) was employed. [d]NMP (2.0 mL) was used instead of THF (1.0 mL).

DOI: 10.1021/acs.orglett.5b02021
Org. Lett. 2015, 17, 4678−4681

was treated with 2.2 equiv of TMPZnCl·LiCl and then quenched with D_2O. ^1H NMR analysis showed >95% D-incorporation at the 5-position of aminotriazole **1k**, which indicates that the zinc species was formed readily in the reaction but could not undergo transmetalation with PhPdBr due to the steric bulkiness of the mesityl group.

We also examined the Negishi coupling by employing 1-phenyl-substituted aminotriazole **1a** and various aryl or vinyl bromides (Table 3). In most cases, 5 mol % catalyst loading is necessary to achieve high reaction conversion and yield. As shown in Table 3, the Negishi coupling of aminotriazole **1a** with electron-rich 4-bromotoluene (**2b**) and 4-bromoanisole (**2c**) proceeded uneventfully, generating the desired aminotriazole **3l** and **3m** in 90% and 86% yield (Table 3, entries 1 and 2). Electron-deficient aryl bromides such as 4-bromobenzotrifluoride (**2d**) and ethyl 4-bromobenzoate (**2e**) also underwent the Negishi coupling smoothly and produced aminotriazoles **3n** and **3o** in 83% and 85% yield, respectively (Table 3, entries 3–4). The reaction using 3-bromopyridine (**2f**) required 10 mol % catalyst to reach full conversion in 24 h and afforded the desired aminotriazole **3p** in 80% yield (Table 3, entry 5). Unfortunately, mesityl bromide (**2g**) did not generate any detectable product **3q** even with 10 mol % catalyst loading, which can be attributed to its significant steric hindrance (Table 3, entry 6). However, when less sterically hindered 2-bromotoluene (**2h**) was subjected to the Negishi coupling, the desired coupling product **3r** was isolated in 67% yield, which attests that the steric effect has a profound impact on the Negishi reaction (Table 3, entry 7). Gratifyingly, vinyl bromides, such as bromomethylenecyclohexane (**2i**) and *β*-bromostyrene (**2j**) successfully afforded excellent 90% and 95% yield of the desired 1,5-disubstituted aminotriazoles **3s** and **3t** (Table 3, entries 8 and 9). To our excitement, 4-bromo-*N*-methylbenzamide (**2k**), a secondary amide containing a relatively acidic proton, also underwent the Negishi coupling smoothly, producing the desired product **3u** in 91% yield, albeit in need of 3.3 equiv of TMPZnCl·LiCl to fully deprotonate all three acid protons in both reactants **1a** and **2k** (Table 3, entry 10).

The benzoyl group on the 3-position amino group can be readily removed in the presence of an acid. For example, 3-aminotriazole **3a** was treated with 5 equiv of 6 M aqueous sulfuric acid in MeTHF at 80 °C, successfully producing the deprotected 3-aminotriazole **4** in 75% yield (eq 3). Therefore, one can



envision that a wide spectrum of 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles with the amino group free of substitution can be achieved in only two steps from aminotriazoles **1** and aryl or vinyl bromides **2**.

Finally, as demonstrated in eq 4, this process is preparatively useful as the desired Negishi coupling product **3a** was isolated in 93% yield on a 5 g (19 mmol) scale.

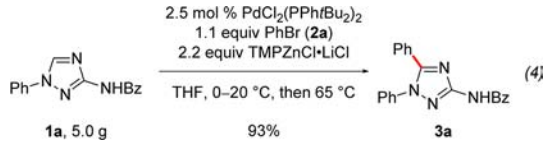
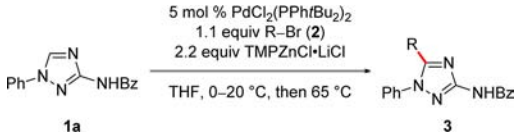
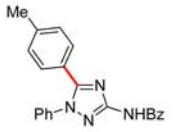
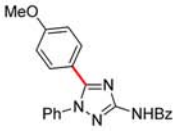
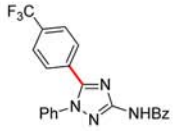
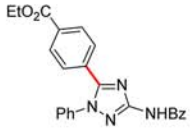
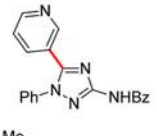
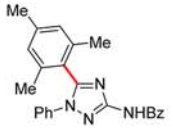
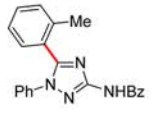
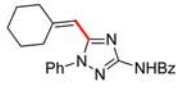
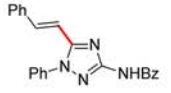
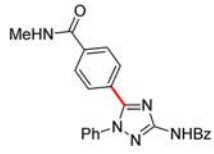


Table 3. Negishi Coupling of Aminotriazoles 1a with Aryl or Vinyl Bromide (2)[a]



entry	halide	product		time (h)	yield (%)[b]
1[c]	**2b**		**3l**	3	90
2	**2c**		**3m**	2	86
3	**2d**		**3n**	3	83
4	**2e**		**3o**	2	85
5[d]	**2f**		**3p**	24	80
6[d]	**2g**		**3q**	24	0
7[d]	**2h**		**3r**	24	67
8	**2i**		**3s**	1	90
9	**2j**		**3t**	1	95
10[e]	**2k**		**3u**	3	91

[a]Reaction conditions: **1a** (0.26 g, 1.0 mmol), $PdCl_2$(PPh-*t*-Bu_2)$_2$ (31 mg, 5 mol %), **2** (1.1 equiv), TMPZnCl·LiCl (0.65 M in THF, 3.4 mL, 2.2 equiv) in THF (1.0 mL), 65 °C. [b]Isolated yield. [c]$PdCl_2$(PPh-*t*-Bu_2)$_2$ (15.5 mg, 2.5 mol %) was employed. [d]$PdCl_2$(PPh-*t*-Bu_2)$_2$ (62 mg, 10 mol %) was employed. [e]TMPZnCl·LiCl (0.65 M in THF, 5.1 mL, 3.3 equiv) was employed.

In summary, we have developed an efficient protocol for the synthesis of 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles via a

DOI: 10.1021/acs.orglett.5b02021
Org. Lett. 2015, 17, 4678–4681

palladium-catalyzed Negishi coupling using in situ generated organozinc intermediates in the presence of a base, TMPZnCl·LiCl. We anticipate that this practical method will provide rapid access to useful quantities of versatile 1,5-disubstituted 3-amino-1*H*-1,2,4-triazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02021.

General experimental procedures, characterization of new compounds, and copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhang.haiming@gene.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We authors thank Drs. Chong Han, Francis Gosselin, and Sushant Malhotra (Genentech, Inc.) for helpful discussions.

■ REFERENCES

(1) (a) Bozo, E.; Szilagyi, G.; Janaky, J. *Arch. Pharm.* **1989**, *322*, 583−587. (b) Naito, Y.; Akahoshi, F.; Takeda, S.; Okada, T.; Kajii, M.; Nishimura, H.; Sugiura, M.; Fukaya, C.; Kagitani, Y. *J. Med. Chem.* **1996**, *39*, 3019−3029.

(2) Baumann, K.; Goetschi, E.; Jolidon, S.; Limberg, A.; Luebbers, T. PCT Int. Appl. 2010052199, 2010.

(3) Marino, J. P.; Fisher, P. W.; Hofmann, G. A.; Kirkpatrick, R. B.; Janson, C. A.; Johnson, R. K.; Ma, C.; Mattern, M.; Meek, T. D.; Ryan, M. D.; Schulz, C.; Smith, W. W.; Tew, D. G.; Tomazek, T. A.; Veber, D. F.; Xiong, W. C.; Yamamoto, Y.; Yamashita, K.; Yang, G.; Thompson, S. K. *J. Med. Chem.* **2007**, *50*, 3777−3785.

(4) Fauchere, J.-L.; Ortuno, J.-C.; Duhault, J.; Boutin, J. A.; Levens, N. European Patent EP 1044970, 2000.

(5) Khadir, A.; Verreault, J.; Averill, D. A. *Arch. Biochem. Biophys.* **1999**, *370*, 163−175.

(6) Ventura, L.; Perez Gonzales, J. A.; Ramon, D. *FEMS Microbiol. Lett.* **1997**, *149*, 207−212.

(7) Clitherow, J. W. European Patent EP 367484, 1990.

(8) Lowe, R. F.; Nelson, J.; Dang, T. N.; Crowe, P. D.; Pahuja, A.; McCarthy, J. R.; Grigoriadis, D. E.; Conlon, P.; Saunders, J.; Chen, C.; Szabo, T.; Chen, T. K.; Bozigian, H. *J. Med. Chem.* **2005**, *48*, 1540−1549.

(9) Temple, C., Jr. In *Triazoles 1,2,4*; Montgomery, J. A., Ed.; John Wiley and Sons: New York, 1981, pp 130−204. (b) Polya, J. B. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon Press: Oxford, UK, 1984; Vol. *5*, pp 733−790.

(10) (a) Katritzky, A. R.; Rogovoy, B. V.; Vvedensky, V. Y.; Kovalenko, K.; Steel, P. J.; Markov, V. I.; Forood, B. *Synthesis* **2001**, *6*, 897−903. (b) Makara, G. M.; Ma, Y.; Margarida, L. *Org. Lett.* **2002**, *4*, 1751−1754. (c) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **2003**, *44*, 7841−7843.

(11) Wong, B.; Stumpf, A.; Carrera, D.; Gu, C.; Zhang, H. *Synthesis* **2013**, *45*, 1083−1093.

(12) Shen, J.; Zhang, H. *Tetrahedron* **2015**, *71*, 6164−6169.

(13) For a review concerning metalations using hindered metal amide bases, see: Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9794−9824.

(14) For reviews on Negishi coupling, see: (a) Negishi, E.-i.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 815−889. (b) Negishi, E.-i. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738−6764.

(15) Zeng, X.; Hu, Q.; Qian, M.; Negishi, E.-i *J. Am. Chem. Soc.* **2003**, *125*, 13636−13637.

(16) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516.

(17) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787−1789.

(18) PEPPSI-*i*Pr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium dichloride. For its application in Negishi coupling, see: Valente, C.; Belowich, M. E.; Hadei, N.; Organ, M. G. *Eur. J. Org. Chem.* **2010**, *23*, 4343−4354.

(19) Under optimal conditions, the reaction of **1a** and chlorobenzene only gave 13% conversion in 24 h.

DOI: 10.1021/acs.orglett.5b02021
Org. Lett. 2015, 17, 4678−4681