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# Efficient Synthesis of 1,4-Diaryl-5-methyl-1,2,3-triazole, A Potential mGluR1 Antagonist, and the Risk Assessment Study of Arylazides

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**Abstract:**

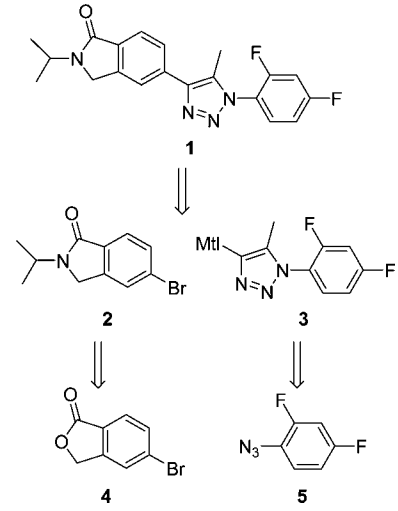
**A concise and practical synthesis of a 1,4-diaryl-5-methyl-1,2,3-triazole is described. A mGluR1 antagonist 1 was prepared with one-pot operation by the Negishi coupling reaction between two building blocks, 5-bromophthalimidine (2) and 1-aryl-5-methyl-4-triazolylzinc (3-*Zn*). Bromide 2 was synthesized via *N*-selective cyclization of *o*-hydroxymethylbenzamide 8 easily prepared from phthalide 4. Zinc species 3-*Zn* was generated in situ by transmetalation of 1-aryl-4-magnesio-5-methyltriazole (3-*Mg*), which in turn was generated by the regioselective click chemistry between 2,4-difluorophenylazide (5) and propynylmagnesium bromide. The risk assessment of potentially explosive arylazides is also mentioned.**

## 1. Introduction

Schizophrenia is one of the most common psychiatric diseases. Prevalence of the disease is about 1% of the total population over the age of 18. The patient population is 2.2 million in the US and 51 million worldwide with an incidence of 100,000 patients/year in US and 1.5 million patients/year worldwide. About $65 billion a year is spent for direct treatment, social and family costs (30% being direct costs). Atypical antipsychotics such as clozapine, risperidone and olanzapine which share $D_2/5HT_{2A}$ antagonism dominate the market. While the introduction of atypical antipsychotics has greatly improved symptoms of schizophrenia, 20−30% of patients do not respond well to these drugs and over one-third has a relapse of symptoms following chronic use. Atypical antipsychotics are relatively extrapyramidal motor side effect-free, however, long-term treatment increases the risk of motor depression and body weight gain. Therefore, there is still a significant need for a new class of antipsychotics. Recently we found the triazole compound **1** which was identified as a potent and selective mGluR1 antagonist[1] could be a novel target to treat schizophrenia.[2]

Compound **1** consists of phthalimidine unit **2** and triazole moiety **3** connected with sp2-sp2 carbon bond. The most efficient approach to **1** appeared to be the coupling reaction between *N*-isopropyl-5-bromophthalimidine (**2**) and 1-aryl-4-metala-5-methyltriazole **3**. As to the preparation of *N*-isopropyl-5-bromophthalimidine (**2**), phthalide **4** is thought to be an appropriate raw material. And the other coupling partner, 1-aryl-4-metala-5-methyltriazole **3** would be prepared by regioselective click chemistry between 2,4-difluorophenylazide (**5**) and propynylmetal reagent. Herein we wish to report the process development of compound **1**. As handling of a large amount of potentially explosive aryazides is a serious risk factor, we carried out a risk assessment study and the results are described.

***Scheme 1.*** **Retrosynthetic analysis**




## 2. Results and Discussion

Following our synthetic strategy (Scheme 1), we began to establish efficient and robust procedures for each reaction. Also, the risk assessment study of potentially explosive arylazides was conducted to develop safe enough procedures for a large-scale synthesis.

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(1) (a) Satow, A.; Maehara, S.; Ise, S.; Hikichi, H.; Fukushima, M.; Suzuki, G.; Kimura, T.; Tanaka, T.; Ito, S.; Kawamoto, H.; Ohta, H. *J. Pharmacol. Exp. Ther.* **2008**, *326*, 577. (b) Suzuki, G.; Kimura, T.; Satow, A.; Kaneko, N.; Fukuda, J.; Hikichi, H.; Sakai, N.; Maehara, S.; Kawagoe-Takaki, H.; Hata, M.; Azuma, T.; Ito, S.; Kawamoto, H.; Ohta, H. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 1144, and references cited therein.

(2) (a) Ohta, H.; Sato, A.; Kimura, T.; Suzuki, G.; Kawamoto, H. PCT Int. Appl. WO 2007007909 A1 20070118, 2007. (b) Kawamoto, H.; Ito, S.; Satoh, A.; Nagatomi, Y.; Hirata, Y.; Kimura, T.; Suzuki, G.; Sato, A.; Ohta, H. PCT Int. Appl. WO 2005085214 A1 20050915, 2005.

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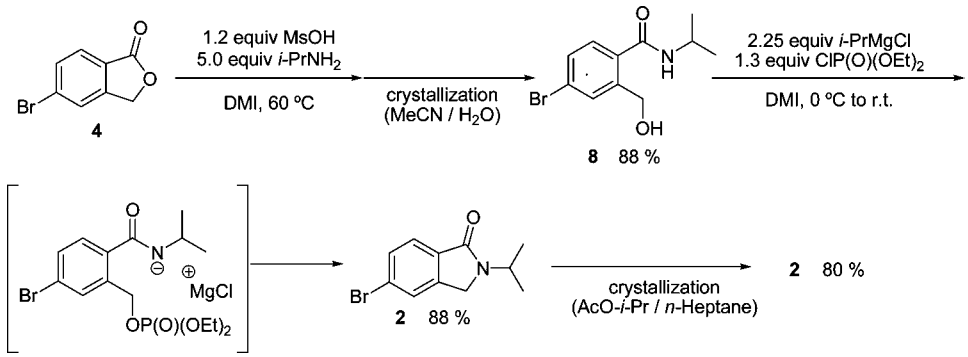
***Scheme 2.*** **Preparation of *N*-isopropyl-5-bromophthalimidine**

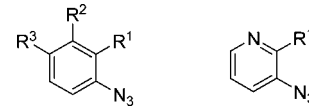



**2.1. Preparation of *N*-Isopropyl-5-bromophthalimidine (2).** The synthesis of the targeted phthalimidine **2** was achieved by *N*-selective cyclization of *o*-hydroxymethylbenzamide **8** which was recently reported by our group.[3] The elaboration of the *o*-hydroxymethylbenzamide **8** was readily accomplished by aminolysis of phthalide **4** in the presence of MsOH at mild temperature.[4] It was found that the amount of MsOH greatly affected the aminolysis. For instance, when an excess of MsOH (2.0 equiv) was employed, phthalide **4** was recovered quantitatively as a result of hydrolysis of imino-ester which was formed by *O*-cyclization of the *o*-hydroxymethylbenzamide **8**. Thus, phthalide **4** was treated with 5.0 equiv of isopropylamine in the presence of 1.2 equiv of MsOH in 1,3-dimethyl-2-imidazolidinone (DMI) at 60 °C for 3 h to give *o*-hydroxymethylbenzamide **8** in 88% isolated yield. The *o*-hydroxymethylbenzamide **8** was then treated with 2.25 equiv of isopropylmagnesium chloride followed with 1.3 equiv of $ClP(O)(OEt)_2$ in DMI to give the phthalimidine **2** in 70% isolated yield.

**2.2. Synthesis of Triazole Moiety and Risk Assessment Study of Arylazides.** After establishing the efficient synthetic method for 5-bromophthalimidine **2**, we next focused on the synthesis of 1,2,3-triazole **3**. For the construction of 1,2,3-triazoles, 1,3-dipolar cycloaddition of organic azides and alkynes is quite often used.[5] However, employing organic azides raises safety concerns since organic azides are known to be heat- and shock-sensitive compounds of varying degrees of stability and sensitive to traces of strong acids and metallic salts which may catalyze explosive decomposition.[6] For example, phenylazide is a distillable compound at considerably reduced pressure; however, phenylazide explodes when heated at ambient pressure and, occasionally, at lower pressure.[7] Thus, a risk assessment study of 2,4-difluorophenylazide (**5**) was necessary prior to the large-scale synthesis.

*2.2.1. Thermal Analysis Study of Arylazides.* We first assessed the thermal stability of 2,4-difluorophenylazide (**5**) to identify an approximate exothermic initiation temperature with differential scanning calorimetry (DSC) measurement. Other arylazide compounds[8] were also assessed for comparison (Table 1). It was found that arylazides had a potentially very large exothermic energy which initiated above 100 °C with a rapid rate of heat release (entry 1, Table 1).

***Table 1.*** **Thermal analysis study of arylazides[a]**



| entry | $R^1$ | $R^2$ | $R^3$ | init. temp. [°C] | size [kcal/mol] |
|---|---|---|---|---|---|
| 1 | F | H | F | 115 | 56 |
| 2 | H | H | H | 140 | 46 |
| 3 | F | H | H | 125 | 84 |
| 4 | H | F | H | 135 | 69 |
| 5 | H | H | F | 130 | 80 |
| 6 | Cl | H | H | 120 | 77 |
| 7 | H | H | Cl | 140 | 79 |
| 8 | Cl | H | Cl | 110 | 69 |
| 9 | $NO_2$ | H | H | 75, 200 | 30, 80 |
| 10 | F | | | 100 | 66 |
| 11 | Cl | | | 85 | 46 |

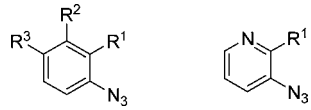
[a] Exothermic activity was evaluated up to a minimum of 300 °C in the closed Tantalum cell (Heat rate: 5 °C/min).

*2.2.2. Drop Weight Testing.* We next performed drop weight testing, or an impact resistance test where weights are dropped on the specimen from varying heights, to determine the possibility of shock sensitivity of arylazides (Table 2). Most of the arylazides including 2,4-difluorophenylazide (**5**) (entry 1, Table 2) showed positive results; explosion occurred with a blast sound, smoke, smell and discoloration (entries 1−7, Table 2). A more detailed study of the 2,4-difluorophenylazide (**5**) proved that **5** is a highly shock sensitive compound (Table 3). The positive result was observed even at 5 kg·cm impact (entry 6, Table 3). However, when the azide **5** was diluted with organic solvents, it was found that the solutions had a safe enough operational window of shock tolerance (entries 7−9, Table 3).

*2.2.3. Advanced Reactive System Screening Tool (ARSST) Test.* 2,4-Difluorophenylazide (**5**) proved to have a potentially very large exothermic energy and be a highly shock sensitive.

(3) Tsuritani, T.; Kii, S.; Akao, A.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2006**, 801.
(4) For $AlCl_3$-catalyzed aminolysis of lactone, see: Lesimple, P.; Bigg, D. C. H. *Synthesis* **1991**, 306.
(5) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1−176. (b) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, pp 1069−1109. (c) Fan, W.-Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 4, pp 101−126.
(6) Boyer, J. H.; Moriarty, R.; de Darwent, B.; Smith, P. A. S. *Chem. Eng. News* **1964**, *42*, 6.
(7) Lindsay, R. O.; Allen, C. F. H. *Org. Synth.* **1942**, *22*, 96.
(8) All arylazides were synthesized with Sandmeyer reaction from the corresponding arylamines.

***Table 2.*** **Drop weight testing[a]**




| entry | $R^1$ | $R^2$ | $R^3$ | state[b] | results[c] |
|---|---|---|---|---|---|
| 1 | F | H | F | L | + |
| 2 | H | H | H | L | + |
| 3 | F | H | H | L | + |
| 4 | H | F | H | L | + |
| 5 | H | H | F | L | + |
| 6 | Cl | H | H | L | + |
| 7 | H | H | Cl | L | + |
| 8 | Cl | H | Cl | S | − |
| 9 | $NO_2$ | H | H | S | − |
| 10 | F | | | S | − |
| 11 | Cl | | | S | − |

[a] Test conditions: volume 20 mg (solid) or 30 $\mu$g (liquid), temp. ambient temperature, height 60 cm (solid) or 30 cm (liquid), weight 5 kg, impact 300 kg·cm (solid) or 150 kg·cm (liquid). [b] L: liquid, S: solid. [c] +: positive, −: negative.

***Table 3.*** **Drop weight testing of 2,4-difluorophenyazide[a]**

| entry | state | impact [kg·cm] | results[b] |
|---|---|---|---|
| 1 | neat | 150 | + |
| 2 | | 100 | + |
| 3 | | 50 | + |
| 4 | | 20 | + |
| 5 | | 10 | + |
| 6 | | 5 | + |
| 7 | THF solution (25.9 wt %) | 150 | − |
| 8 | heptane solution (26.4 wt %) | 150 | − |
| 9 | MTBE solution (29.4 wt %) | 150 | − |

[a] Test conditions: volume 30 $\mu$g, temp. ambient temperature, weight 5 kg. [b] +: positive, −: negative.

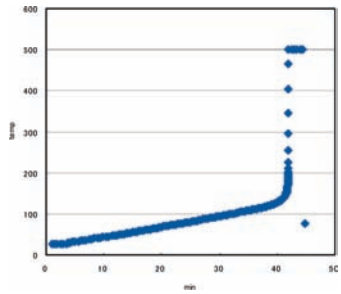


***Figure 1.*** **Time vs temperature (neat 5).**

Thus an ARSST test[9] was conducted to obtain more information. ARSST data yielded critical experimental knowledge of the rates of temperature and pressure increases during the exothermic decomposition of **5**, thereby providing reliable energy and gas release rates which can be applied directly to full scale process conditions. ARSST results are summarized in Figures 1, 2, 3, and 4 and Tables4 and5. Temperature scanning mode test showed that neat 2,4-difluorophenylazide (**5**) had a potential to explode upon heating with significant rapid temperature and pressure increase around 200 °C (Figures 1 and 2, and Table 4). On the other hand, the MTBE solution of 2,4-difluorophenylazide (**5**) was proved not to have an explosive

(9) Burelbach, J. P.; Miller, A. E. *Proc. NATAS Annu. Conf. Therm. Anal. Appl.* **2001**, *29*, 567.

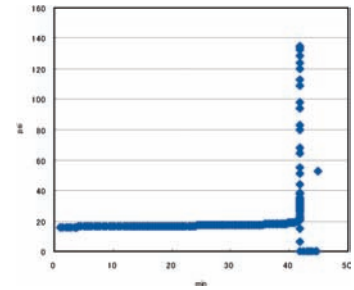


***Figure 2.*** **Time vs pressure (neat 5).**

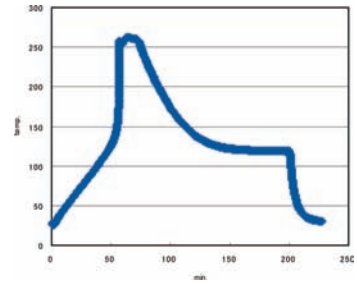


***Figure 3.*** **Time vs temperature (MTBE solution 5).**

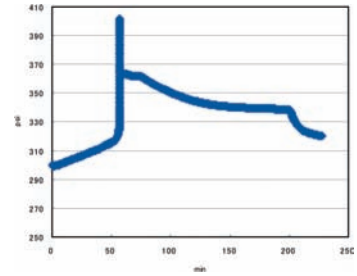


***Figure 4.*** **Time vs pressure (MTBE solution 5).**

***Table 4.*** **ARSST test (temperature scanning mode) results of 5[a]**

| sample | initial pressure [psi] | peak temp [°C] | MAX. d$T$/d$t$ [°C/min] | MAX. d$P$/d$t$ [psi/min] | MAX. pressure increase [psi] | residual pressure [psi] |
|---|---|---|---|---|---|---|
| neat | 15 | >500[b] | 338,194 | 90,736 | NA[c] | NA[c] |
| MTBE solution (29.4 wt %) | 298 | 294 | 3,682 | 6,144 | 122 | 9.4 |

[a] Conditions; sample mass 5.6 mL (neat) or 7.0 mL (MTBE solution), heating rate 2 °C/min, acquisition frequency 1 °C or 1 psi or 0.5 min, heater shut off 500 °C or 500 psi or 500 min. [b] A full measurement of temperature could not be detected due to heater shutdown criteria. [c] A full measurement of pressure and residual pressure could not be detected due to rupture of rupture disk.

nature. Although relatively high temperature and pressure increase were also observed around 200 °C, the temperature and pressure were decreased after the culmination without an explosion (Figure 3 and 4, and Table 4). Isothermal ages test proved that the MTBE solution of **5** was relatively stable at 50−110 °C range; max dT/dt was less than 2.0 °C/min, max dP/dt was less than 0.3 psi/min and max pressure increase was less than 30 psi (Table 5).

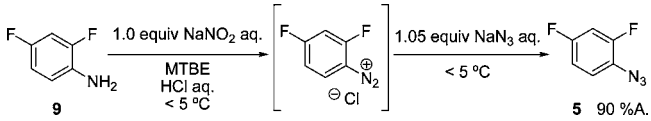
*2.2.4. Synthesis of 2,4-Difluorophenylazide in Large Scale.* On the basis of the results of the risk assessment studies (*vide supra*), we focused on the synthesis of **5** on a large scale. For the synthesis of arylazides, the Sandmeyer reaction of 2,4-difluoroaniline was adopted.[10] The Sandmeyer reaction was superior to other approaches such as hydrazine chemistry[11] and copper-catalyzed azidation[12] in view of yield, purity, and milder

***Table 5.*** **ARSST test (isothermal age mode) results of the MTBE solution of 5**

| entry | initial pressure [psi] | age temp [°C] | MAX. d*T*/d*t* [°C/min] | MAX. d*P*/d*t* [psi/min] | MAX. pressure increase [psi] | residual pressure [psi] |
|---|---|---|---|---|---|---|
| 1 | 301 | 50 | 1.45 | 0.21 | 5.56 | 1.37 |
| 2 | 302 | 70 | 1.99 | 0.21 | 11.90 | 5.79 |
| 3 | 303 | 90 | 1.99 | 0.26 | 19.05 | 7.82 |
| 4 | 301 | 110 | 1.77 | 0.24 | 26.71 | 12.51 |

[a] Conditions; sample mass 7.0 mL (MTBE solution), hours aged 16 h, acquisition frequency 1 °C or 1 psi or 0.5 min, heater shut off 500 °C or 500 psi or 500 min.

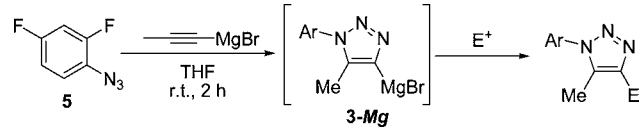
***Scheme 3.*** **Synthesis of 2,4-difluorophenylazide (5)**




reaction conditions although it entailed the use of the toxic reagent, $NaN_3$. It was found that the reaction should be conducted in the presence of MTBE to prevent potentially hazardous separation of the highly hydrophobic 2,4-difluorophenylazide (**5**) from the aqueous media. Eventually we were able to establish an efficient procedure for the synthesis of 2,4-difluorophenylazide (**5**) under the company criteria for judging safety of operations (for the company criteria, see Experimental Section and references cited there). 2,4-Difluoroaniline (**9**) was treated with 1.0 equiv of 15% $NaNO_2$ aq in 1.5 N HCl aq and MTBE at between −10 to 5 °C (initial addition temperature −10 °C) followed with 1.05 equiv of 12% $NaN_3$ aq at between −10 to 5 °C (initial addition temperature −10 °C) to give a MTBE solution of 2,4-difluorophenylazide (**5**) in 90% assay yield (Scheme 3).

**2.3. Regioselective Synthesis of 4-Metallatriazole and Its Application to Palladium-Catalyzed C−C Bond-Coupling Reaction.** After establishing the safe-enough protocol for the synthesis of 2,4-difluorophenylazide (**5**),[13] we turned our attention to the regioselective synthesis of 4-metallatriazole **3**. Sharpless et al., had already reported that regioselective 1,3-dipolar addition of azide and alkynyl Grignard reagent proceeded smoothly at ambient temperature.[14] Accordingly, 1,3-dipolar addition of 1-propynylmagnesium bromide and 2,4-difluorophenylazide (**5**) was examined (Table 6). The reaction proceeded smoothly at ambient temperature, and afforded the corresponding triazole in high yield as a single regioisomer. The reaction with crude MTBE solution of azide **5** also resulted in acceptable yield of triazole (entry 2). Triazole **3-*Mg*** still has active magnesium at the 4-position which can be utilized for

***Table 6.*** **Regioselective [3 + 2] annulation[a]**




| entry | electrophile | $E^+$ | yield[b] [%] |
|---|---|---|---|
| 1 | $H_2O$ | $H^+$ | 95 |
| 2[c] | $H_2O$ | $H^+$ | 96 |
| 3 | $D_2O$ | $D^+$ | 91 |
| 4 | NBS | $Br^+$ | 89 |

[a] The reaction was performed with 1.05 equiv of a THF solution of propynylmagnesium bromide. [b] Isolated yield. [c] A MTBE solution of 2,4-difluorophenylazide (**5**) (25.5 wt %) was used instead of neat one.

the following coupling reaction.[15] Thus, we examined consecutive reactions for the construction of triazole moiety and subsequent C−C bond formation.

After extensive investigation, we found the $Pd_2(dba)_3$-Xantphos catalyst system to work very well for this one-pot reaction.[16] However, when this developed method was applied to the reaction of **3-*Mg*** and phthalimidine **2**, the lactam moiety of **2** was not tolerant of the reaction conditions. It was discovered that this issue was able to be circumvented by the use of less nucleophilic **3-*Zn*** reagent which was easily prepared from **3-*Mg***. Thus, the MTBE solution of 2,4-difluorophenylazide (**5**) was treated with 1.07 equiv of propynylmagnesium bromide in THF at ambient temperature for 2 h followed with 1.10 equiv of $ZnCl_2$ to give the intermediate **3-*Zn***. The resulting **3-*Zn*** was treated with 0.98 equiv of the phthalimidine **2** in the presence of 1.5 mol % of $Pd_2(dba)_3$ and 3.0 mol % of Xantphos at 55 °C for 6 h to give the desired 1,4-diaryl-5-methyltriazole **1** in 89% assay yield (Scheme 4). Crystallization from MTBE furnished the crude **1** as a pale-yellow colored crystal with 98.5% purity on HPLC, residual palladium 66 ppm and the undesired kinetically favored crystal form. Recrystallization from AcOEt/heptane in the presence of $PBu_3$ (5.0 equiv with respect to palladium catalyst) to reduce palladium content and control crystal form furnished the pure **1** as a white crystal with 99.0% purity on HPLC, residual palladium 18 ppm and the desired thermodynamically favored crystal form.

## 3. Conclusion

In conclusion, a concise and practical synthesis of 1,4-diaryl-5-methyl-1,2,3-triazole has been established. For the synthesis of 5-bromophthalimidine intermediate **2** and 1,4-diaryl-5-methyl-1,2,3-triazole **1**, we successfully developed a new and concise procedure. Both developed reactions are adaptable not only for a large-scale synthesis but also for a wide variety of substrates.[3,16] The risk assessment study of arylazide **5** proved that neat arylazides have a very large exothermic energy, are highly shock sensitive, and have potential to explode upon heating, whereas a diluted solution of **5** was safe enough to handle.


(10) Odlo, K.; Hentzen, J.; dit Chabert, J. F.; Ducki, S.; Gani, O. A.; Sylte, I.; Skrede, M.; Florenes, V. A.; Hansen, T. V. *Bioorg. Med. Chem.* **2008**, *16*, 4829.

(11) Iranpoor, N.; Firouzabadi, H.; Nowrouzi, N. *Tetrahedron Lett.* **2008**, *49*, 4242.

(12) Jacob, A.; Ulf, M.; Fredrik, B.; Xifu, L. *Synlett* **2005**, 2209.

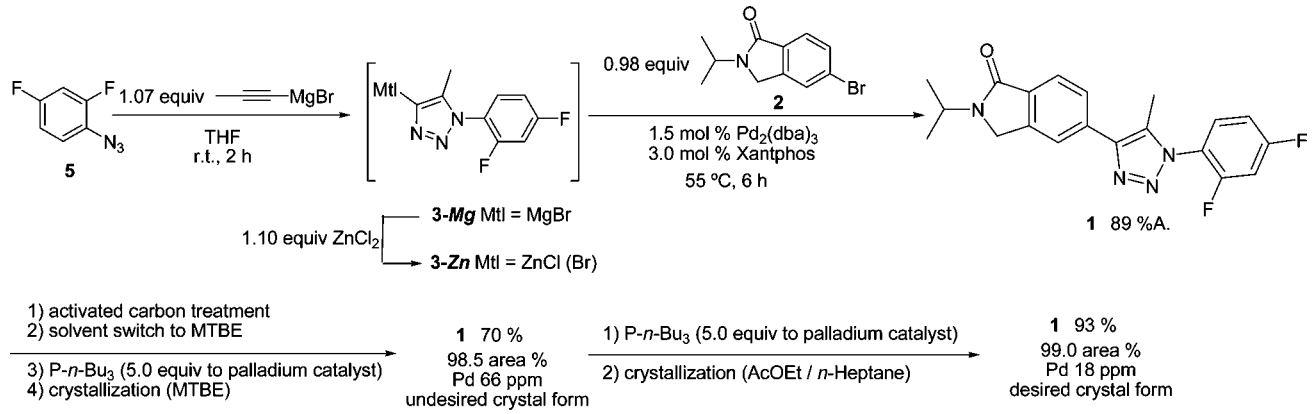
(13) The obtained 2,4-difluorophenyazide (**5**) was labile against oxygen and light. The solution of azide **5** took on deep black color unless it was stored under light shielding, nitrogen atmosphere and low temperature. For the photochemistry of fluorinated aryl azides, see: Leyva, E.; Munoz, D.; Platz, M. S. *J. Org. Chem.* **1989**, *54*, 5938.

(14) (a) Krasiñski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237. (b) Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1967**, *3*, 968. (c) Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1967**, *3*, 2241. (d) Akimova, G. S.; Chistokletov, V. N.; Petrov, A. A. *Zh. Org. Khim.* **1968**, *4*, 389.

(15) The reactions of the resulting 4-magnesiotriazole **3-*Mg*** with various electrophiles has already reported by Sharpless (ref 14); however, the transition metal-catalyzed reactions of **3-*Mg*** with arylhalides were unexplored.

(16) For detailed information of this one-pot coupling reaction, see: Akao, A.; Tsuritani, T.; Kii, S.; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2007**, 31.

***Scheme 4.*** **Coupling reaction of *N*-isopropyl-5-bromophthalimidine with 4-zincio-1,2,3-triazole 3-*Zn***




## 4. Experimental Section

**4.1. General.** All reagents were purchased and used without any further purification. $^1$H and $^{13}$C NMR spectra were taken in $CDCl_3$ at 400 and 100 MHz, respectively.

**4.2. *N*-Isopropyl-4-bromo-2-hydroxymethylbenzamide (8).** To an 80 L reactor were charged DMI (16.0 L) and phthalide **4** (8.0 kg, 37.6 mol). The resulting slurry was cooled to 0 °C, and then *i*-Pr$NH_2$ (16.1 L, 187.8 mol) was added to the slurry. MsOH (2.9 L, 45.1 mol) was slowly added over about 1.5 h, keeping the temperature range between 0 to 15 °C during the addition. The slurry was heated at 60 °C for 3 h, and then the resulting solution was allowed to cool to ambient temperature.

To a 150 L vessel was charged half the volume of the above crude solution, water (12.0 L) and MeCN (32.0 L). To the solution was added 12.0 g (amide **8**) of seed. After stirring for 1 h, water (64.0 L) was added dropwise over 1 h to the resulting suspension and stirred for 3 h. The same operations were conducted with the rest of the crude solution. The amide **8** was collected by filtration, washed with water (20.0 L), and dried under vacuum at 60 °C for 36 h to give 9.0 kg of **8** in 87.7% yield. $^1$H NMR ($CDCl_3$) 7.56 (s, 1H), 7.49 (d, $J$ = 8.2 Hz, 1H), 7.37 (d, $J$ = 8.2 Hz, 1H), 6.20−6.13 (bs, 1H), 4.56 (s, 2H), 4.26 (septet, $J$ = 6.5 Hz, 1H), 1.27 (d, $J$ = 6.5 Hz, 6H).

**4.3. *N*-Isopropyl-5-bromophthalimidine (2).** To a 150 L vessel equipped with dropping funnel were charged DMI (40.0 L) and amide **8** (8.0 kg, 29.4 mol). The resulting solution was cooled to −10 °C, and then 1.98 M of *i*-PrMgCl (33.1 L, 65.5 mol, 2.23 equiv to amide **8**) was added dropwise over 1.5 h, keeping the temperature range between −10 to 5 °C during the addition. The resulting solution was warmed to ambient temperature and stirred for 0.5 h. The solution was cooled to 0 °C, and then $ClP(O)(OEt)_2$ (6.6 kg, 38.2 mol, 1.3 equiv to amide **8**) was added dropwise over about 50 min, keeping the temperature range between 0 to 14 °C during the addition. The mixture was warmed to ambient temperature and stirred for 14 h. The resulting solution was quenched by slow addition of 2 N HCl aq (40.0 L) at between 10 to 25 °C. The mixture was extracted with *i*-PrOAc (40.0 L × 2), and the combined *i*-PrOAc extracts were washed with water (40.0 L × 2) and 20% brine (8.0 L). The combined organic layer was assayed by HPLC measurement (6.8 kg assay, 90.5% yield). Azeotropic dehydration with *i*-PrOAc was conducted until the water content was below 500 ppm, and then *i*-PrOAc (3.4 L) was added. To the suspension was added heptane (45.6 L), and the suspension was heated at 50 °C. The resulting solution was cooled down to 41 °C, and then 6.8 g of seed (phthalimidine **2**) was added. After stirring for 1 h at 41 °C, the suspension was slowly cooled down to −6 °C over about 5 h, and stirred for 1 h. The desired product was collected by filtration, washed with heptane (17.2 L), and dried under vacuum at 60 °C for 20 h. to give 4.8 kg of **2** in 64.8% yield. $^1$H NMR ($CDCl_3$) 7.70 (d, $J$ = 7.9 Hz, 1H), 7.61 (s, 1H), 7.60 (d, $J$ = 7.9 Hz, 1H), 4.65 (septet, $J$ = 6.8 Hz, 1H), 4.32 (s, 2H), 1.29 (d, $J$ = 6.8 Hz, 6H). $^{13}$C NMR ($CDCl_3$) 166.89, 142.96, 132.37, 131.44, 126.12, 125.64, 124.99, 44.60, 42.76, 20.77. IR (neat, cm$^{-1}$) 1674, 1609, 1449, 1406, 1275, 1236, 1174, 1060, 867, 839, 768, 674, 620.

**4.4. 2,4-Difluorphenylazide (5).** The reaction was conducted with a 50 L vessel (2 batches). **Arylazide 5 must not be isolated since it is highly shock sensitive and thermally unstable. Considering the perilousness for the explosive nature of arylazide 5 with metal and heat, the reaction temperature was controlled by an oil bath, not an internal heating/cooling pipe, and was limited to temperatures lower than 40 °C. The reaction vessel was covered with aluminum foil to obscure light since arylazide 5 is decomposed by light.**[13] To a 50 L vessel were added 1.5 N HCl aq (14 L), MTBE (3.5 L), and 2,4-difluoroaniline (900 g, 6.97 mol). The mixture was cooled down to −10 °C. $NaNO_2$ aq (480 g, 6.97 mol in 2.70 L water) was added carefully, keeping the temperature range between −10 to 5 °C during the addition.[17] After completion of the addition, the mixture was stirred for 15 min at between 0 to 5 °C. $NaN_3$ aq (480 g, 7.32 mol in 3.60 L water) was added carefully keeping the temperature range between −10 to 5 °C.[18] After completion of the addition, the mixture was stirred for 30 min at between 0 to 5 °C. To the

(17) The addition of the sodium nitrite aqueous solution ***should be*** controlled with stirring and cooling throughout due to the moderate size of heat generation,−18.6 kcal/mol (aniline) of aniline with an adiabatic temperature rise of +6.4 K.

(18) Sodium azide in water is in equilibrium with hydrogen azide, a highly volatile and shock sensitive material. Aqueous solutions greater than 15 wt % $NaN_3$ could pose a thermal hazard. Therefore, ***it is recommended*** to prepare a more dilute sodium azide aqueous solution, the temperature of the sodium azide aqueous solution ***must be*** maintained cold,−5 °C to avoid volatilization of hydrogen azide (boiling point of hydrogen azide is 36−38 °C), and the addition of the sodium azide aqueous solution ***should be*** controlled with stirring and cooling throughout due to the moderate size of heat generation,−52.0 kcal/mol (aniline) of aniline with an adiabatic temperature rise of + 17.0 K. The appropriate venting capacity ***must be*** calculated to deal with nitrogen gas generation during addition of sodium azide aqueous solution.

mixture was added MTBE (6.98 L). After phase separation,[19] the organic layer was washed with 1 N NaOH (4.50 L) and water (4.50 L) successively. Azeotropic dehydration with MTBE (~22.50 L)[20] was conducted until the water content became lower than 500 ppm. 2,4-Difluorophenylazide (**5**) was obtained in 970 g assay, 90% assay yield with 86.24 area % purity on HPLC. The product solution should be stored away from sources of heat, under light shielding and nitrogen gas atmosphere. It should be stored refrigerated if it is not used immediately. It should not be stored for a prolonged period of time. $^1$H NMR ($CDCl_3$) 7.05−7.00 (m, 1H), 6.90−6.85 (m, 2H). $^{13}$C NMR ($CDCl_3$) 124.22, 121.63, 121.56, 112.01, 111.97, 111.83, 111.79, 105.49, 105.30, 105.27, 105.09. IR (neat, $cm^{-1}$) 2137, 2104, 1604, 1504, 1436, 1333, 1270.

**4.5. 1H-Isoindol-1-one, 5-[1-(2,4-difluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl]-2,3-dihydro-2-(1-methylethyl) (1).** The reaction was performed with an 80 L vessel (two batches). To the stirred THF solution of 8.9 wt % propynylmagnesium bromide (12.35 kg, 6.61 mol), was added a MTBE solution of azide **5** (25.5 wt %, 3.76 kg, 958 g assay, 6.18 mol) over 20 min.[21] The combined mixture was stirred for 2 h at around 25 °C. Then, THF solution of 17.3 wt % $ZnCl_2$[22] (water content 412 ppm, 5.35 kg, 926 g assay, 6.79 mol) was added over 30 min, keeping the temperature range between 20 to 30 °C[23] and stirred overnight. To the resulting dark-brown solution were added phthalimidine **2** (1.54 kg, 6.05 mol) and an active palladium catalyst solution which was prepared by mixing of $Pd_2(dba)_3$ (84.8 g, 0.0926 mol) and Xantphos (107 g, 0.185 mol) in THF (2.55 kg) then by degassed by vacuum/$N_2$-fill cycles 3 times, and stirred for 2 h. The reaction mixture was degassed and stirred at 55 °C for 6 h. Then the reaction mixture was cooled to ambient temperature. To the solution, was added 1 N HCl (13.48 L).[24] The organic layer was extracted by MTBE (8.60 kg). The organic extract was washed successively with 1 N HCl (13.53 L) and water (13.27 kg). The organic layer was extracted against the combined acidic aqueous layers by THF/MTBE (THF 2.87 L + MTBE 2.40 kg). The combined organic layers were washed with 5% $NaHCO_3$ (13.22 and 6.64 kg) and then with water (13.62 kg) and analyzed by HPLC (1.97 kg assay, 89% yield from phthalimidine **2**).

The obtained solution was combined with an another batch of **1** and treated with Darco KB-100 mesh (850 g) for 1 h. After a filtration of the mixture, the residual charcoal was washed with THF (22.3 kg). The solution was switched to MTBE with addition-and-concentration. During the course of solvent switching, seed of **1** (7.4 g) was added. The resultant slurry was heated to 50−55 °C, $PBu_3$ (344 g, 1.70 mol, 5 equiv with respect to palladium catalyst) was added, and the batch aged for 3 h. Then the slurry was cooled to ambient temperature and stirred for overnight. The mixture was filtered, and the collected solid was washed with ice-cold MTBE and dried under a nitrogen atmosphere. The coupled product **1** was obtained as pale-yellow colored crystals (2471 g, 70% recovery, 98.5 area % purity on HPLC, 66 ppm of Pd content, undesired crystal form). Loss in mother liquid was 716 g assay (20%) and rinsed solution was 163 g assay (4.6%). To control the crystal form and reduce Pd content, the following recrystallization was performed. The obtained crystals were dissolved in EtOAc (55.75 kg) and stirred for 1 h. The solution was concentrated under reduced pressure, and the resulted slurry was heated to 90 °C for dissolution of crystals, then $PBu_3$ (84.9 mL, 0.34 mol, 0.05 equiv to the crude crystals) was added. The slurry was cooled to 65−70 °C, and seed of **1** (15.7 g) was added. The slurry was stirred for 1 h, and heptane (28.75 kg) was slowly added with over 80 min. Then the resulting slurry was stirred for 1 h., and was cooled gradually to ambient temperature and stirred for overnight. The slurry was filtered, and the collected solid was washed with heptane/EtOAc (9:1, 13.19 L) and dried under vacuum at 50 °C overnight. The desired compound **1** was obtained as almost colorless crystals (2293 g, 93% recovery, 99.0 area % purity on HPLC, 18 ppm of Pd content, desired crystal form). $^1$H NMR ($CDCl_3$) $\delta$ 8.00 (s, 1H), 7.94 (d, $J$ = 7.6 Hz, 1H), 7.81 (dd, $J$ = 7.6, 1.2 Hz, 1H), 7.61−7.55 (m, 1H), 7.16−7.09 (m, 2H), 4.72 (septet, $J$ = 6.8 Hz, 1H), 4.42 (s, 2H), 2.45 (d, $J$ = 1.2 Hz, 3H), 1.33 (d, $J$ = 6.8 Hz, 6H). $^{13}$C NMR ($CDCl_3$) $\delta$ 167.35, 164.89, 164.78, 162.36, 162.25, 157.88, 157.76, 155.33, 155.20, 143.64, 141.82, 133.87, 132.73, 131.94, 129.87, 129.76, 126.46, 123.70, 121.39, 120.44, 120.40, 120.30, 120.26, 112.70, 112.66, 112.47, 112.43, 105.58, 105.35, 105.32, 105.09, 44.99, 42.63, 20.72, 9.50, 9.47. IR (neat, $cm^{-1}$) 1679, 1662, 1625, 1519, 1456, 1411, 1264, 1144, 963, 850, 811, 780, 610. HRMS $[M + H]^+$ $m/z$ calcd for $C_{20}H_{18}N_{4O}F_2$ + H 369.1527; Found, 369.1531.

(19) The aqueous waste before aqueous NaOH wash operations ***must be*** treated by aqueous NaOH.

(20) The batch temperature during the concentration must be kept as low as possible and not approach temperatures above 40 °C as there is a large exotherm present in the concentrate. A high alarm set at 50 °C should be provided for the reactor. Emergency cooling should be applied if the alarm goes off. Dilution of batch with cold MTBE is to be done if the batch temperature approaches 70 °C. The product solution may not be concentrated to a level significantly higher than that tested (29.4 wt % MTBE solution).

(21) The addition of MTBE solution of arylazide **5** to the vessel ***should be*** controlled with stirring and cooling throughout. The heat release was measured to be−37.1 kcal/mol (azide) of the arylazide with an adiabatic temperature rise of +32.9 K. A high temperature alarm of 50 °C should be set on the reactor.

(22) Preparation for the THF solution of $ZnCl_2$: To a 20 L vessel, THF (6.20 kg) was charged, and $ZnCl_2$ (1300 g) was added keeping the temperature range between 20 to 30 °C. To the solution, molecular sieves 4 Å (1300 g) was added. The resultant solution was left at rest for overnight at ambient temperature, and its supernatant solution was used for the coupling reaction.

(23) The addition of zinc chloride THF solution to the vessel ***should be*** controlled with stirring and cooling throughout. The heat release was measured to be−8.4 cal/g (batch) with an adiabatic temperature rise of +19.9 K.

(24) The addition of 1 N HCl to the vessel ***should be*** controlled with stirring and cooling throughout. The heat release was measured to be−5.6 cal/g (batch) with an adiabatic temperature rise of +9.5 K.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## Supporting Information Available

Detailed ARSST study results and spectra chart of compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.


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