Facile One-Pot Synthesis of Monosubstituted 1-Aryl-1*H*-1,2,3-triazoles from Arylboronic Acids and Prop-2-ynoic Acid (= Propiolic Acid) or Calcium Acetylide (= Calcium Carbide) as Acetylene Source

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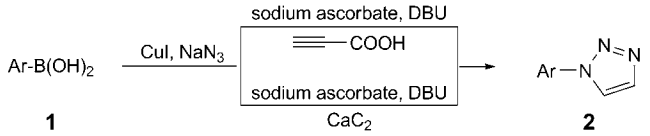
The synthesis of monosubstituted 1-aryl-1*H*-1,2,3-triazoles was achieved in a one-pot reaction from arylboronic acids and prop-2-ynoic acid or calcium acetylide (=calcium carbide), respectively, as a source of acetylene, with yields ranging from moderate to excellent (*Scheme 1*, *Table 2*). The reaction conditions were successfully applied to arylboronic acids, including analogs with various functionalities. Unexpectedly, the 1,2,3-triazole moiety promoted a regioselective hydrodebromination (*Scheme 2*).

Introduction. – The 1*H*-1,2,3-triazole unit is an important structure unit in a number of pharmaceuticals, agrochemicals, and chemical reagents, and has also found widespread applications in the fields of material science and molecular structure design [1]. Deriving from the robust Cu-catalyzed *Huisgen* 1,3-dipolar cycloaddition, 1,4-disubstituted 1*H*-1,2,3-triazoles can be synthesized efficiently [2]. However, there are few efficient methodologies described concerning the synthesis of 1-monosubstituted 1*H*-1,2,3-triazoles *via* this useful 'click reaction'. One strategy was the decarboxylation of triazoles bearing a carboxylic acid substituent, but the reaction required extreme temperatures and long reaction times [3]. Another method was the cycloaddition of azides to acetylene [2f] and its equivalents such as acetylides (ethynyltrimethylsilane and ethynyltributylstannane) [4] and vinyl compounds (vinyl acetate, vinyl ethers, vinylamines, and vinyl sulfoxides) [5]. Very recently, calcium acetylide (=calcium carbide; CaC_2), and prop-2-ynoic acid (= propiolic acid) were also reported to be used as a safe and inexpensive acetylene source [6]. However, all of these methods employed poisonous and potentially explosive organic azides as starting materials, which has limited their applications in the synthesis of 1-monosubstituted 1*H*-1,2,3-triazoles.

Herein, we would like to describe a convenient and efficient one-pot protocol for the preparation of monosubstituted 1-aryl-1*H*-1,2,3-triazoles **2** (*Scheme 1*). In this method, arylboronic acids **1** were involved as the starting materials to generate organic

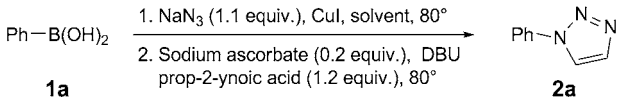
Scheme 1. *Synthesis of Monosubstituted 1-Aryl-1*H*-1,2,3-triazoles* **2**



azides *in situ* according to *Liu*'s report [7], and CaC_2 or prop-2-ynoic acid were used as the source of acetylene, respectively. Thus, the isolation of the poisonous and unstable organic azides was avoided.

Results and Discussion. – An initial investigation of the reaction conditions was conducted with phenylboronic acid (**1a**; 0.3 mmol), NaN_3 (1.1 equiv.), and prop-2-ynoic acid (1.2 equiv.) as the starting materials, in which decarboxylation may occur *in situ* [6c]. The reaction was carried out in the presence of different amounts of CuI and additives (DBU (=1,8-diazabicyclo[5.4.0]undec-7-ene), Et_3N, and Et_2NH) in different solvents (DMF and CH_2Cl_2) at 80°. However, the first step of the reaction failed when pure DMF was applied as the solvent (*Table 1*, *Entry 1*). When dioxane or DMSO was used as the solvent, the reaction worked, but the yield of the triazole **2a** was low (*Entries 2* and *3*). To our surprise, the improved yield of 40% of **2a** was obtained when H_2O alone was used as the medium (*Entry 4*). Inspiringly, the product yield was improved further when a moderate amount of H_2O was added to DMF as a co-solvent (*Entries 5–8*). The yield was increased up to 68% when CuI (0.1 equiv.), NaN_3 (1.1 equiv.), sodium ascorbate (0.2 equiv.), DBU (0.5 equiv.), and prop-2-ynoic acid (1.2 equiv.) were added to the solvent DMF/H_2O 6:1. Additionally, the first step of the

Table 1. *Optimization of the Synthesis of 1-Phenyl-1*H-*1,2,3-triazole* (**2a**)[a])



1a **2a**

Entry	CuI [equiv.]	Base (equiv.)	Solvent (*v*/*v*)	Yield [%] of **2a**[b])
1[c])	0.1	DBU (0.5)	DMF	0
2	0.1	DBU (0.5)	dioxane	32
3	0.1	DBU (0.5)	DMSO	36
4	0.1	DBU (0.5)	H_2O	40
5	0.1	DBU (0.5)	DMF/H_2O 2:1	48
6	0.1	DBU (0.5)	DMF/H_2O 4:1	56
7	0.1	DBU (0.5)	DMF/H_2O 6:1	68
8	0.1	DBU (0.5)	DMF/H_2O 8:1	51
9	0.1	Et_3N (0.5)	DMF/H_2O 6:1	37
10	0.2	DBU (0.5)	DMF/H_2O 6:1	79
11[d])[e])	0.2	DBU (0.5)	DMF/H_2O 6:1	88
12[f])[e])	0.2	DBU (0.5)	DMF/H_2O 6:1	80
13[d])[e])	0.2	DBU (0.3)	DMF/H_2O 6:1	72
14[d])[e])	0.3	DBU (0.5)	DMF/H_2O 6:1	82
15[d])[e])	0.2	DBU (0.8)	DMF/H_2O 6:1	76
16[d])[g])	0.2	DBU (0.5)	DMF/H_2O 6:1	42

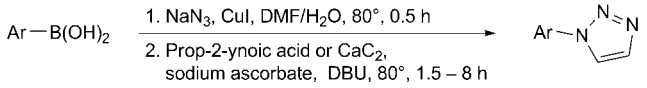
[a]) Conditions unless indicated otherwise: a mixture of $PhB(OH)_2$ (0.3 mmol), NaN_3 (0.33 mmol), and CuI in solvent (2 ml) was heated to 80° and stirred until $PhB(OH)_2$ was consumed. After the mixture was cooled to r.t., DBU, sodium ascorbate (0.06 mmol), and prop-2-ynoic acid were added, and the reaction was then conducted at 80° until PhN_3 was consumed (TLC monitoring). [b]) Yield of isolated product. [c]) The second step was not conducted. [d]) 0.45 mmol of prop-2-ynoic acid was used. [e]) 0.16 mmol of sodium ascorbate was used. [f]) 0.54 mmol of propiolic acid was used. [g]) No sodium ascorbate was used.

reaction ran smoothly and finished within 0.5 h (*Entry 7*). The base Et_3N seems not as efficient as DBU under these conditions (*Entry 9*). Our study also showed that increasing the amount of CuI to 0.2 equiv. or prop-2-ynoic acid to 1.5 equiv. was beneficial to the yield (*Entries 10* and *11*), while an overabundance of CuI or prop-2-ynoic acid was unfavorable (*Entries 12* and *14*). Reducing the amount of DBU caused a decline of the yield (*Entry 13*) as well. An additionally important discovery was that the presence of sodium ascorbate in the reaction mixture was absolutely necessary to obtain a higher yield, as the yield dropped near to half in the absence of sodium ascorbate (*Entry 16*). Finally, the yield of **2a** was increased to up to 88% when the optimal conditions were applied to the reaction at 80°, *i.e.*, CuI (0.2 equiv.), NaN_3 (1.1 equiv), sodium ascorbate (0.4 equiv.), DBU (0.5 equiv.), and prop-2-ynoic acid (1.5 equiv.) in DMF/H_2O 6:1 (*Entry 11*).

The optimized conditions were then also applied to CaC_2 instead of prop-2-ynoic acid as an alternative source of acetylene for the synthesis of the monosubstituted 1-phenyl-1*H*-1,2,3-triazole (**2a**; *Table 2*, *Entry 1*); under the effect of CuI, phenyl azide was formed *in situ* and then treated with CaC_2, generating the expected product in 86% yield.

This methodology (with prop-2-ynoic acid or CaC_2) led to monosubstituted 1*H*-1,2,3-triazoles, while polysubstituted 1*H*-1,2,3-triazoles were generated in previously described methods [8], in which arylboronic acids and NaN_3 were also involved as the

Table 2. *Synthesis of 1-Momosubstitued 1,2,3-Triazoles* **2**[a])



1 **2**

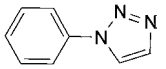
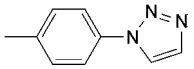
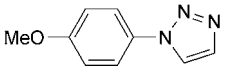
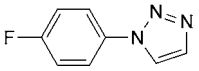
Entry	Ar	Product **2**	Yield [%][b])	Time [h][b])	Yield [%][c])	Time [h][c])
1	Ph	**2a**	88	4	86	4.5
2	4-Me–C_6H_4	**2b**	89	4	86	5
3	3-Me–C_6H_4	**2c**	85	5	82	6
4[d])	2-Me–C_6H_4	**2d**	76	8	81	7
5	4-MeO–C_6H_4	**2e**	86	4	85	5.5
6	3-MeO–C_6H_4	**2f**	82	5	87	6
7	4-HO–C_6H_4	**2g**	71	4	69	6
8	3-NH_2–C_6H_4	**2h**	72	4	76	4
9	4-CHO–C_6H_4	**2i**	92	2.5	84	3
10	4-F–C_6H_4	**2j**	94	3	93	3
11	3-NO_2–C_6H_4	**2k**	90	1.5	82	2
12	Naphthalen-1-yl	**2l**	69	8	78	7

[a]) Conditions: arylboronic acid **1** (0.3 mmol), NaN_3 (0.33 mmol), and CuI (0.06 mmol) were added to DMF/H_2O 6:1 (2 ml). The mixture was heated to 80° and stirred until the $ArB(OH)_2$ was consumed. After cooling to r.t., DBU (0.15 mmol), sodium ascorbate (0.12 mmol), and prop-2-ynoic acid (0.45 mmol) or CaC_2 (0.45 mmol) were added, and the reaction was then conducted at 80° until the ArN_3 was consumed (TLC monitoring). [b]) Yield of isolated product by using prop-2-ynoic acid, and time of the second step. [c]) Yield of isolated product by using CaC_2, and time of the second step. [d]) Conducted at 120°.

starting materials. Under the optimized reaction conditions, also a series of arylboronic acids was subjected to the reaction with prop-2-ynoic acid and CaC_2, respectively, affording monosubstitued 1-aryl-1*H*-1,2,3-triazoles (*Table 2*). The results showed that arylboronic acids carrying either an electron-donating substituent such as a Me, MeO, OH, or NH_2 group (*Table 2*, *Entries 2–8*) or an electron-withdrawing group including a formyl, F, or NO_2 group (*Entries 9–11*) proceeded successfully. Substrates bearing either an electron-donating or an electron-withdrawing group at the *para*- or *meta*-position gave all the corresponding monosubstitued 1-aryl-1*H*-1,2,3-triazole in good to excellent yields at 80°. Though the arylboronic acids bearing an *ortho*-substituent suffered from a low reaction rate due to the steric hindrance effect (*Entries 4* and *12*), their reaction proceeded successfully by raising the temperature up to 120°. Additionally, groups such as OH, formyl, and NH_2 of the arylboronic acids were tolerated (*Entries 7–9*). It is especially worth noting that this procedure is also suitable for the preparation of 1-aryl-1*H*-1,2,3-triazoles bearing an amino group at the benzene moiety.

Furthermore, the entire procedure of synthesizing 1-aryl-1*H*-1,2,3-triazoles **2** could also be achieved by a one-pot 'one-step' manipulation (*Table 3*). Monosubstitued 1-aryl-1*H*-1,2,3-triazoles with either an electron-donating substituent such as Me or MeO (*Table 3*, *Entries 2 and 3*) or an electron-withdrawing group such as F (*Entry 4*) could be obtained through this one-pot 'one-step' procedure; but the yields were slightly lower than those of the one-pot 'two-step' procedure (*Table 2*).

Table 3. *Synthesis of 1-Aryl-1*H*-1,2,3-triazoles* **2** *by a One-Pot 'One-Step' Procedure*[a])

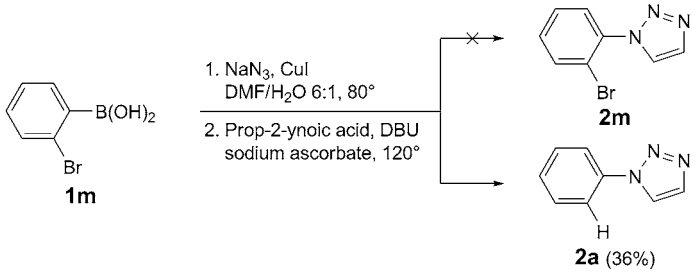
Entry	Product		Yield [%][b])	Time [h][b])	Yield [%][c])	Time [h][c])
1		**2a**	72	4	68	4.5
2		**2c**	75	5	80	6
3		**2e**	66	4	72	5.5
4		**2j**	82	3	86	3

[a]) Conditions: arylboronic acid **1** (0.3 mmol), NaN_3 (0.33 mmol), CuI (0.06 mmol), sodium ascorbate (0.12 mmol), prop-2-ynoic acid (0.45 mmol), or CaC_2 (0.45 mmol) and DBU (0.15 mmol) were added to DMF/H_2O 6:1 (2 ml). The reaction was then conducted at 80° until arylboronic acid and ArN_3 were consumed (TLC monitoring). [b]) Yield of isolated product by using prop-2-ynoic acid and reaction time. [c]) Yield of isolated product by using CaC_2 and reaction time.

Additionally, a copper-catalyzed hydrodebromination directed by the 1,2,3-triazole moiety was observed during the present study. Not the expected 1-(2-bromophenyl)-1*H*-1,2,3-triazole (**2m**) but 1-phenyl-1*H*-1,2,3-triazole (**2a**) was obtained in 36% yield when (2-bromophenyl)boronic acid (**1m**) was used as the substrate (*Scheme 2*).

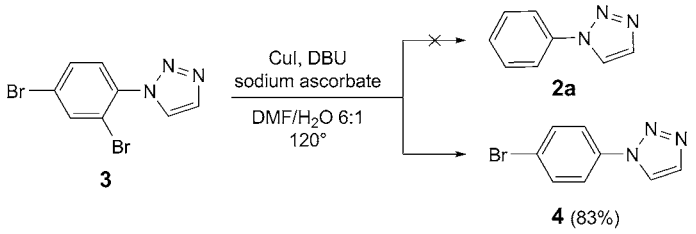
To elucidate the role of the 1,2,3-triazole moiety in this hydrodebromination, 1-(2,4-dibromophenyl)-1*H*-1,2,3-triazole (**3**) was employed directly under the above con-

Scheme 2. *Reaction of (2-Bromophenyl)boronic Acid* (**1m**)



ditions (*Scheme 3*). The product of the debromination was not 1-phenyl-1*H*-1,2,3-triazole (**2a**) but 1-(4-bromophenyl)-1*H*-1,2,3-triazole (**4**, 83% yield). Thus, the 1,2,3-triazole moiety seems to act as the directing group, which promoted the regioselective hydrodebromination of the *ortho*-Br substituent in the substrate.

Scheme 3. *1,2,3-Triazole-Promoted Hydrodebromination of 1-(2,4-Dibromophenyl)-1*H*-1,2,3-triazole* (**3**)



In summary, we demonstrated a facile and efficient protocol for the synthesis of monosubstitued 1-aryl-1*H*-1,2,3-triazoles from arylboronic acids and prop-2-ynoic acid or CaC_2, respectively, as the source of acetylene. This protocol provided a convenient and mild access to these 1*H*-1,2,3-triazoles, which are important heterocyclic compounds in medicinal chemistry and material science. Unexpectedly, a 1,2,3-triazole-promoted regioselective hydrodebromination was observed, and the study of its application is ongoing.

This work was supported by the *Natural Science Foundation of China* (No. 30873153), the *Key Projects of Shanghai in Biomedicine* (No.08431902700), and the *Scientific Research Foundation* of the *State Education Ministry for the Returned Overseas Chinese Scholars.* We would like to thank the Center for Instrumental Analysis, Tongji University, China. We thank Dr. *Y. Hefner* (1278 Avenida Miguel, Encinitas, CA 92024, U.S.A.) for helpful discussion and critical reading as well as editing this manuscript.

Experimental Part

General. Commercially obtained reagents were used without further purification. TLC: *Huanghai* GF_{254} silica-gel coated plates. Column chromatography (CC): SiO_2 (300–400 mesh), at medium pressure. ^{1}H-NMR Spectra: *Bruker-AM-500* spectrometer in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz.

*Monosubstitued 1-Aryl-1*H*-1,2,3-triazoles* **2**: *General Procedure.* A soln. of arylboronic acid **1** (0.3 mmol), NaN_3 (22 mg, 0.33 mmol), and CuI (11 mg, 0.06 mmol) in DMF/H_2O 6:1 (2 ml) was stirred at 80° until **1** was consumed completely (TLC monitoring). Then, the mixture was cooled to r.t., sodium ascorbate (24 mg, 0.12 mmol), prop-2-ynoic acid (32 mg, 0.45 mmol), and DBU (23 mg, 0.15 mmol) were added, and the stirred mixture was heated to 80° until the reaction was completed. The mixture was allowed to cool to r.t., then quenched with H_2O (15 ml), and extracted with AcOEt (3 × 10 ml). The combined org. layer was washed with brine (3 × 5 ml), dried (Na_2SO_4), and concentrated and the crude product purified by CC (silica gel, AcOEt/hexane 1:2): **2**.

*1-Phenyl-1*H*-1,2,3-triazole* (**2a**) [6a]. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.00 (*d*, *J* = 0.9, 1 H); 7.86 (*d*, *J* = 0.9, 1 H); 7.76–7.74 (*m*, 2 H); 7.56–7.53 (*m*, 2 H); 7.45 (*t*, *J* = 16.0, 1 H).

*1-(4-Methylphenyl)-1*H*-1,2,3-triazole* (**2b**) [6a]. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.95 (*d*, *J* = 1.0, 1 H); 7.83 (*d*, *J* = 1.0, 1 H); 7.62 (*d*, *J* = 8.0, 2 H); 7.32 (*d*, *J* = 8.0, 2 H); 2.43 (*s*, 3 H).

*1-(3-Methylphenyl)-1*H*-1,2,3-triazole* (**2c**) [2f]. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.98 (*d*, *J* = 0.7, 1 H); 7.84 (*d*, *J* = 0.7, 1 H); 7.59 (*s*, 1 H); 7.52 (*d*, *J* = 8.0, 1 H); 7.42 (*d*, *J* = 8.0, 1 H); 7.27–7.25 (*m*, 1 H); 2.46 (*s*, 3 H).

*1-(2-Methylphenyl)-1*H*-1,2,3-triazole* (**2d**) [6a]. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.86 (*d*, *J* = 0.9, 1 H); 7.76 (*d*, *J* = 0.9, 1 H); 7.43–7.34 (*m*, 4 H); 2.20 (*s*, 3 H).

*1-(4-Methoxyphenyl)-1*H*-1,2,3-triazole* (**2e**) [2f]. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.91 (*d*, *J* = 0.8, 1 H); 7.83 (*d*, *J* = 0.8, 1 H); 7.64 (*d*, *J* = 6.8, 2 H); 7.03 (*d*, *J* = 6.8, 2 H,); 3.87 (*s*, 3 H).

*1-(3-Methoxyphenyl)-1*H*-1,2,3-triazole* (**2f**) [4c]. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.00 (*s*, 1 H); 7.84 (*s*, 1 H); 7.43–7.36 (*m*, 2 H); 7.27 (*dd*, *J* = 2.3, 7.4, 1 H); 6.98 (*dd*, *J* = 2.4, 8.3, 1 H); 3.88 (*s*, 3 H).

*4-(1*H*-1,2,3-Triazol-1-yl)phenol* (**2g**) [6a]. ^{1}H-NMR (500 MHz, (D_6)DMSO): 9.91 (*s*, 1 H); 8.63 (*d*, *J* = 1.0, 1 H); 7.90 (*d*, *J* = 1.0, 2 H); 7.66 (*q*, *J* = 9.0, 2 H); 6.93 (*d*, *J* = 9.0, 2 H).

*3-(1*H*-1,2,3-Triazol-1-yl)benzenamine* (**2h**) [9a]. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.95 (*d*, *J* = 1.1, 1 H); 7.82 (*d*, *J* = 1.0, 1 H); 7.27 (*t*, *J* = 8.0, 8.0, 1 H); 7.14 (*t*, *J* = 2.1, 2.1, 1 H); 7.02 (*ddd*, *J* = 0.8, 2.0, 8.0, 1 H); 6.73 (*ddd*, *J* = 0.8, 2.3, 8.1, 1 H); 3.95 (*s*, 2 H).

*4-(1*H*-1,2,3-Triazol-1-yl)benzaldehyde* (**2i**) [9b]. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.09 (*s*, 1 H); 8.12 (*d*, *J* = 1.1, 1 H); 8.08 (*d*, *J* = 8.69, 2 H); 7.99 (*d*, *J* = 8.56, 2 H); 7.91 (*d*, *J* = 1.1, 1 H).

*1-(4-Fluorophenyl)-1*H*-1,2,3-triazole* (**2j**) [6a]. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.95 (*d*, *J* = 1.0, 1 H); 7.85 (*d*, *J* = 1.0, 1 H); 7.73 (*d*, *J* = 9.0, 2 H); 7.23 (*d*, *J* = 7.6, 2 H).

*1-(3-Nitrophenyl)-1*H*-1,2,3-triazole* (**2k**) [2f]. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.61 (*t*, *J* = 2.0, 1 H); 8.34–8.31 (*m*, 1 H); 8.23–8.21 (*m*, 1 H); 8.12 (*d*, *J* = 1.0, 1 H); 7.92 (*d*, *J* = 1.0, 1 H); 7.77 (*t*, *J* = 8.2, 1 H).

*1-(Naphthalen-1-yl)-1*H*-1,2,3-triazole* (**2l**) [9c]. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.05–8.02 (*m*, 1 H); 7.98–7.95 (*m*, 3 H); 7.61–7.53 (*m*, 5 H).

*1-(2,4-Dibromophenyl)-1*H*-1,2,3-triazole* (**3**) [9d]. A soln. of 1-azido-2,4-dibromobenzene (277 mg, 1 mmol), CaC_2 (128 mg, 2 mmol), CuI (38 mg, 0.2 mmol), and sodium ascorbate (80 mg, 0.4 mmol) in MeCN/H_2O 3:1 (6 ml) was stirred at 80° until the starting 1-azido-2,4-dibromobenzene was consumed completely (TLC monitoring). The mixture was allowed to cool to r.t. and the reaction quenched with H_2O (15 ml). The mixture was extracted with AcOEt (3 × 10 ml), and the combined org. layer washed with brine (3 × 5 ml), dried (Na_2SO_4), and concentrated and the crude product purified by CC (silica gel, AcOEt/hexane 1:2): **3** (83%). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.97 (*s*, 1 H); 7.94 (*d*, *J* = 2.0, 1 H); 7.87 (*s*, 1 H); 7.64 (*dd*, *J* = 2.0, 8.4, 1 H); 7.44 (*d*, *J* = 8.46, 1 H).

Regioselective Hydrodebromination of **3** *Affording* **4**. To a soln. of **3** (91 mg, 0.3 mmol) in DMF/H_2O 6:1 (2 ml) was added CuI (11 mg, 0.06 mmol), sodium ascorbate (24 mg, 0.12 mmol), and DBU (23 mg, 0.15 mmol). The mixture was heated to 120° and stirred until **3** was consumed completely (TLC monitoring). The mixture was cooled to r.t., and then H_2O (10 ml) was added. The mixture was extracted with AcOEt (3 × 10 ml), the combined org. layer washed with brine (3 × 5 ml), dried (Na_2SO_4), and concentrated, and the crude product purified by CC (SiO_2, AcOEt/hexane 1:2): 1-(4-bromophenyl)-1*H*-1,2,3-triazole [2f] (**4**; 83%). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.98 (*s*, 1 H); 7.87 (*s*, 1 H); 7.68 (*d*, *J* = 9.1, 2 H); 7.65 (*d*, *J* = 9.1, 2 H).

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Received June 18, 2011