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Palladium-Catalyzed Direct Arylations of 1,2,3-Triazoles with Aryl Chlorides using Conventional Heating

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Abstract: Generally applicable, palladium-catalyzed direct arylations of 1,2,3-triazoles with aryl chlorides were accomplished through conventional heating at reaction temperatures of 105–120 °C. Thereby, intra- and intermolecular C–H bond functionalizations were achieved with a variety of differently substituted chlorides as electrophiles, bearing numerous valuable functional groups.

Keywords: arylation; C–C coupling; C–H activation; palladium; triazoles

Introduction

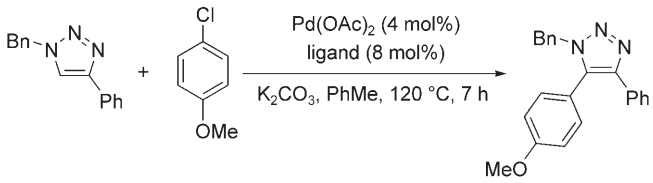
1,2,3-Triazoles are important substructures of various compounds with biological activities of relevance to medicinal chemistry. Thus, various strategies for their synthesis have been devised, with Huisgen's 1,3-dipolar [3+2] cycloadditions of azides and alkynes[1] being the most commonly used approach.[2] The efficient rate enhancement and excellent regioselectivity achieved with either copper[3,4] or ruthenium catalysts,[5] allowed more recently for their widespread applications in diverse research areas, ranging from bioorganic chemistry to material sciences.[6] While these catalytic [3+2] cycloadditions proceeded efficiently and highly regioselectively with terminal alkynes, the corresponding transformations of internal alkynes to fully substituted 1,2,3-triazoles were found to be either not generally applicable or gave rise to mixtures of regioisomers.[5,7–9] Alternative methodologies for their syntheses, such as metalations of disubstituted triazoles, or cycloadditions with either deprotonated C–H acidic compounds or magnesiated terminal alkynes,[2] often rely on stoichiometric amounts of highly reactive organometallic reagents, and therefore show significant limitations in scope.

The direct functionalization of C–H bonds[10–14] in 1,2,3-triazoles could constitute an attractive alternative to traditional cross-couplings with organometallic reagents because of its ecologically and economically benign nature. Among the known direct arylations of electron-rich heteroarenes, the majority has been accomplished under rhodium or palladium catalyses, applying aryl iodides, bromides, or triflates as electrophiles.[15–17] Thus, Gevorgyan and co-workers communicated recently on direct arylations of 1,2,3-triazoles with aryl *bromides*.[18] However, aryl chlorides are arguably the most useful single class of halides due to their lower cost and the wider diversity of (commercially) available compounds.[19,20] As part of our program on the use of more easily accessible and less expensive electrophiles, such as chlorides[21–23] and tosylates,[24] in direct arylation reactions,[25,26] we became interested in probing palladium-catalyzed direct arylations of 1,2,3-triazoles with aryl chlorides.[27] A very recent report by Oshima and co-workers on a *non-thermal microwave effect* on palladium-catalyzed direct arylations of 1,2,3-triazoles with aryl chlorides,[28] prompted us to disclose our own results on the direct arylations of 1,2,3-triazoles with aryl chlorides through conventional heating.[27] Importantly, these studies highlight that microwave heating and a reaction temperature of 250 °C are not mandatory for efficient catalysis to proceed. Instead, C–H bond functionalizations of 1,2,3-triazoles with aryl chlorides can be conveniently achieved through conventional heating at significantly milder reaction temperatures of 105–120 °C.

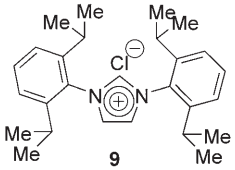
Results and Discussion

At the outset of our studies, we optimized reaction conditions for the challenging palladium-catalyzed direct arylation of triazole **1a** with the electron-rich, thus for an oxidative addition electronically-deactivated, aryl chloride **2a** employing conventional thermal heating. Interestingly, our studies showed that polar aprotic solvents, such as NMP, DMF, or DMA, were found to provide less satisfactory results, while 1,4-dioxane and toluene as solvents along with K_2CO_3 as base allowed for efficient catalysis. Subsequently, we probed the effect of various phosphine and carbene ligands in the palladium-catalyzed direct arylation, employing economical $Pd(OAc)_2$ as palladium source and the challenging chloride **2a** as electrophile (Table 1). Notably, a thermal reaction did not occur under phosphine ligand-free reaction conditions (entry 1). Aryl-substituted tertiary monophosphine ligands **4–6** gave also no conversion of the starting materials using conventional heating (entries 2–4). Similarly, commonly used bidentate phosphine ligands **7** and **8** (entries 5, and 6) or N-heterocyclic carbene precursors, like imidazolium salt **9** (entry 7), were found ineffective.

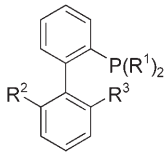
Table 1. Optimization studies for the palladium-catalyzed direct arylation of triazole **1a** with electron-rich chloride **2a**.[a]



1a **2a** **3aa**

Entry	Ligand	Yield
1	-	-
2	PPh_3 (**4**)	-
3	$P(o\text{-Tol})_3$ (**5**)	-
4	$P(p\text{-Tol})_3$ (**6**)	-
5	BINAP (**7**)	-
6	dppf (**8**)	-
7	 **9**	-
8	$(t\text{-Bu})_3PHBF_4$ (**10**)	10%
9	**11a**	10%
10	**11b**	47%
11	**11c**	48%
12	PCy_3 (**12**)	53%
13	**12**	96%[b]
14	**12**	92%[c]
15	**12**	84%[d]

[a] *Reaction conditions:* **1a** (1.0 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (4.0 mol%), ligand (8.0 mol%), K_2CO_3 (2.0 mmol), PhMe (2 mL), 120 °C, 7 h. GC yields using *n*-heptadecane as internal standard.
[b] 20 h at 120 °C.
[c] 1,4-Dioxane (2 mL), 24 h at 105 °C; isolated yield.
[d] 22 h at 105 °C.



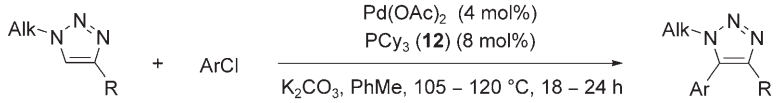
R^1 = *i*-Pr; R^2, R^3 = H: **11a**
R^1 = Cy; R^2 = NMe_2; R^3 = H: **11b**
R^1 = Cy; R^2, R^3 = OMe: **11c**

Figure 1. General structure of monophosphine biaryl ligands **11**.

However, more electron-rich, alkyl-substituted tertiary phosphines enabled palladium-catalyzed direct arylations with the electron-rich chloride **2a** (entries 8–12). While phosphonium salt **10** (entry 8) and monophosphine biaryl ligands **11a–c** (entries 9–11, and Figure 1) gave rather unsatisfactory yields, commercially available phosphine **12** proved superior in the thermal palladium-catalyzed direct arylation of triazole **1a** (entries 12, and 13). This highly active catalytic system enabled even an efficient direct arylation to occur at a reaction temperature of 105 °C (entries 14 and 15).

With this optimized catalytic system in hand, we probed its scope in the direct arylation of *N*-alkyl-substituted 1,2,3-triazoles **1** with various aryl chlorides **2** (Table 2). 1,2,3-Triazoles with substituents on either aromatic group of **1a** were efficiently converted, and the corresponding products **3ab** and **3ac** could be isolated in high yields (entries 1, and 2). Simple *N*-(*n*-alkyl)-substituted triazoles were efficiently arylated as well with conventional heating (entry 3). However, 1,2,3-triazoles with two *n*-alkyl-substituents reacted rather sluggishly under our reaction conditions. Here, a significant rate-acceleration was accomplished with catalytic amounts of pivalic acid[29–31] as additive (entries 4 and 5). With respect to the electrophile, electron-rich aryl chlorides could generally be employed (entries 1–5), even when being more sterically hindered through *ortho*-substitution (entry 6). Importantly, a variety of valuable functional groups was tolerated by the catalytic system. Thus, aryl chlorides displaying an ester substituent were efficiently converted (entries 7 and 8). Remarkable, a chloride with an enolizable ketone gave rise chemoselectively to the desired product **3aj** in high yields of isolated product (entries 9–11). Here, as in the palladium-catalyzed direct arylation with chloride **2f** bearing a cyano group (entries 12 and 13), substoichiometric amounts of pivalic acid proved to generate a more effective catalyst. A comparable isolated yield was obtained in 1,4-dioxane as solvent at 105 °C (entry 10). Finally, we

Table 2. Palladium-catalyzed direct arylations of *N*-alkyl-substituted triazoles **1** with aryl chlorides **2**.[a]



1 **2** **3**

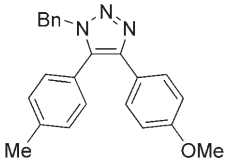
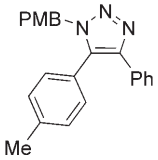
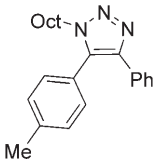
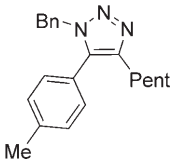
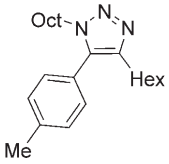
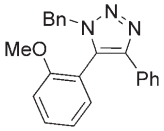
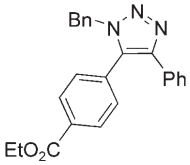
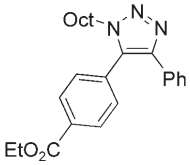
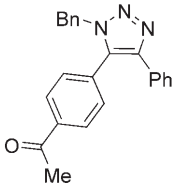
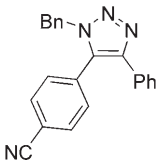
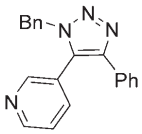
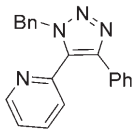
Entry	Alk	R		Ar		Product		Isolated Yield
1	Bn	4-$MeOC_6H_4$	**1b**	4-MeC_6H_4	**2b**		**3ab**	74%
2	PMB	Ph	**1c**	4-MeC_6H_4	**2b**		**3ac**	80%
3	Oct	Ph	**1d**	4-MeC_6H_4	**2b**		**3ad**	70%
4	Bn	Pent	**1e**	4-MeC_6H_4	**2b**		**3ae**	66%[b]
5	Oct	Hex	**1f**	4-MeC_6H_4	**2b**		**3af**	68%[b]
6	Bn	Ph	**1a**	2-$MeOC_6H_4$	**2c**		**3ag**	95%
7	Bn	Ph	**1a**	4-$EtO_2CC_6H_4$	**2d**		**3ah**	70%
8	Oct	Ph	**1d**	4-$EtO_2CC_6H_4$	**2d**		**3ai**	63%
9 10 11	Bn	Ph	**1a**	4-$Me(O)CC_6H_4$	**2e**		**3aj**	(37%)[c] 63%[d] 67%[b]

Table 2. (Continued)

Entry	Alk	R		Ar		Product		Isolated Yield
12								(41%)[c]
13								71%[b]
	Bn	Ph	**1a**	4-NCC_6H_4	**2f**		**3ak**	
14	Bn	Ph	**1a**	3-py	**2g**		**3al**	58%
15	Bn	Ph	**1a**	2-py	**2h**		**3am**	82%

[a] *Reaction conditions:* **1** (0.50–1.00 mmol), **2** (0.75–1.50 mmol), $Pd(OAc)_2$ (4.0 mol%), **12** (8.0 mol%), K_2CO_3 (1.00–2.00 mmol), PhMe (2 mL), 120 °C, 18–24 h; PMB = 4-$MeOC_6H_4CH_2$.
[b] *t*-$BuCO_2H$ (30 mol%).
[c] GC conversion.
[d] *t*-$BuCO_2H$ (30 mol%), 1,4-dioxane (2 mL), 105 °C, 18 h.

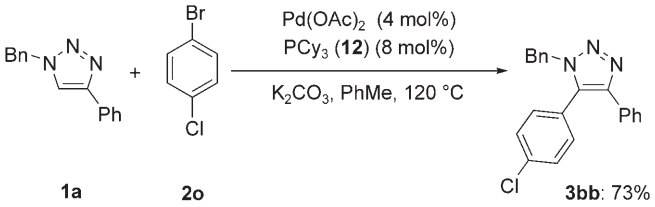
found that heteroaromatic chlorides could be employed in these thermal direct arylation reactions as well. Thus, 3- and even 2-chloropyridine (**2g**, and **2h**) gave rise to triazoles **3al** and **3am**, respectively, in good yields (entries 14 and 15).

Regioselective palladium-catalyzed direct arylations of arenes bearing Lewis-basic *N*-containing directing groups are well established.[14,15,32] With respect to *N*-aryl-substituted 1,2,3-triazoles **1** this might result in a competitive arylation of the carbo- and heterocyclic moieties. Therefore, we tested the regioselectivity of thermal palladium-catalyzed direct arylations with *N*-aryl-substituted 1,2,3-triazoles **1** (Table 3). Notably, 1,2,3-triazoles **1** with *N*-aryl groups being either unsubstituted (entry 1), or *meta*- (entries 2–4) as well as *ortho*-substituted (entries 5–14) were converted to single regioisomers with excellent selectivities through arylations of the electron-rich heterocycles. Thereby, a variety of important functional groups, such as ester (entries 1–3, and 5–8), ketones (entries 9–11), or a silyl substituent (entry 8), was tolerated. Also the challenging electron-rich aryl chlorides were efficiently transformed into the desired fully substituted 1,2,3-triazoles in high yields (entries 4 and 12–14).

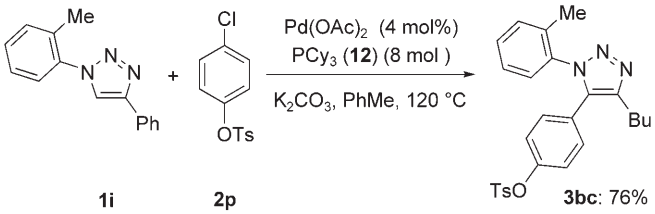
Subsequently, we tested the chemoselectivity of thermal palladium-catalyzed direct arylations of 1,2,3-triazoles within competition experiments. Thus, bromochlorobenzene **2o** reacted highly selectively, giving rise to 1,2,3-triazole **3bb** in good isolated yield through coupling of the aryl bromide functionality (Scheme 1).

However, the chloride was found to be a significantly better leaving group when compared with a tosylate, as illustrated by the highly selective coupling of electrophile **2p** to afford triazole **3bc** (Scheme 2). Thus, these experiments suggest the following order in reactivity of leaving groups in the electrophile: Br > Cl > OTs.

In agreement with this reactivity trend, the direct arylation of 1,2,3-triazole **1a** proceeded highly efficiently with bromide **13** and chloride **2b** as electro-

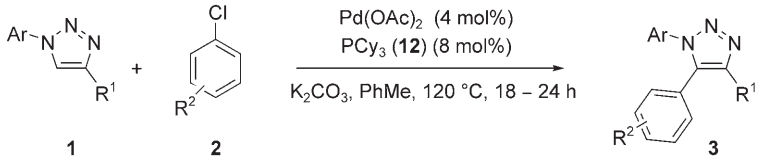


Scheme 1. Chemoselective catalytic direct arylation with electrophile **2o**.



Scheme 2. Chemoselective catalytic direct arylation with electrophile **2p**.

Table 3. Palladium-catalyzed direct arylations of *N*-aryl-substituted triazoles **1** with aryl chlorides **2**.[a]



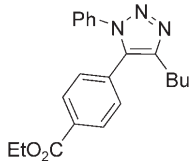
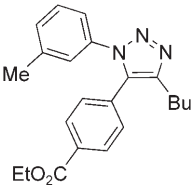
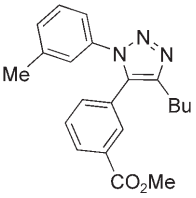
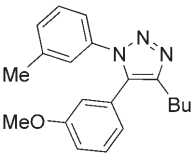
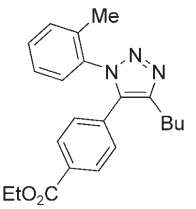
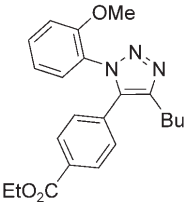
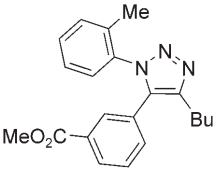
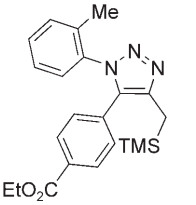
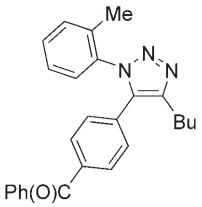
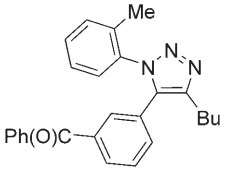
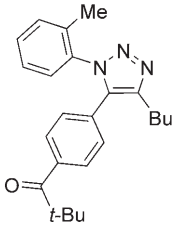
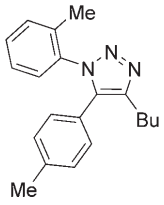
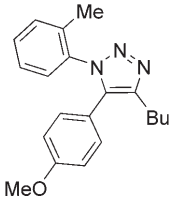
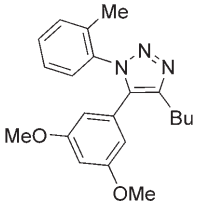
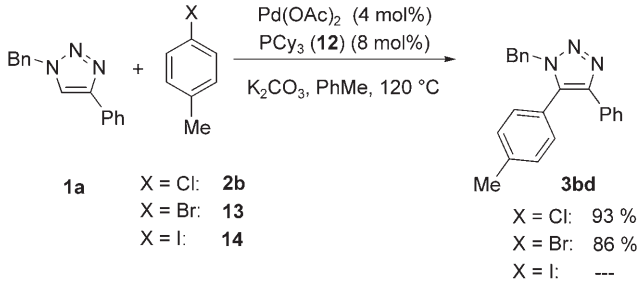
Entry	Ar	R^1		R^2		Product		Isolated Yield
1	Ph	Bu	**1g**	4-CO_2Et	**2d**		**3an**	65%
2	3-MeC_6H_4	Bu	**1h**	4-CO_2Et	**2d**		**3ao**	65%
3	3-MeC_6H_4	Bu	**1h**	3-CO_2Me	**2i**		**3ap**	69%
4	3-MeC_6H_4	Bu	**1h**	3-OMe	**2j**		**3aq**	60%
5	2-MeC_6H_4	Bu	**1i**	4-CO_2Et	**2d**		**3ar**	68%
6	2-$MeOC_6H_4$	Bu	**1j**	4-CO_2Et	**2d**		**3as**	62%
7	2-MeC_6H_4	Bu	**1i**	3-CO_2Me	**2i**		**3at**	96%
8	2-MeC_6H_4	CH_2TMS	**1k**	4-CO_2Et	**2d**		**3au**	47%

Table 3. (Continued)

Entry	Ar	R^1		R^2		Product		Isolated Yield
9	2-MeC_6H_4	Bu	**1i**	4-C(O)Ph	**2k**		**3av**	95%
10	2-MeC_6H_4	Bu	**1i**	3-C(O)Ph	**2l**		**3aw**	80%
11	2-MeC_6H_4	Bu	**1i**	4-C(O)-*t*-Bu	**2m**		**3ax**	95%
12	2-MeC_6H_4	Bu	**1i**	4-Me	**2b**		**3ay**	70%
13	2-MeC_6H_4	Bu	**1i**	4-OMe	**2a**		**3az**	87%
14	2-MeC_6H_4	Bu	**1i**	3,5-$(OMe)_2$	**2n**		**3ba**	90%

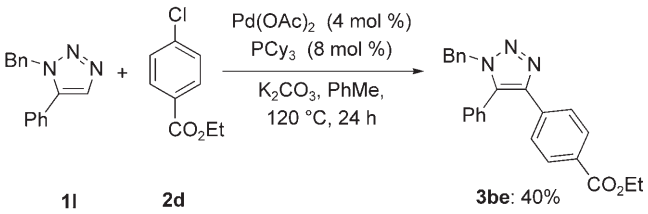
[a] *Reaction conditions:* **1** (0.50–1.00 mmol), **2** (0.75–1.50 mmol), $Pd(OAc)_2$ (4.0 mol%), **12** (8.0 mol%), K_2CO_3 (1.00-2.00 mmol), PhMe (2 mL), 120 °C, 18–24 h.



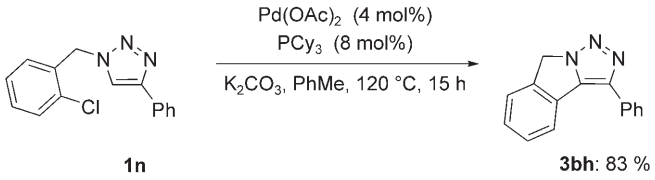
Scheme 3. Catalytic direct arlyation with different halides as electrophiles.

philes (Scheme 3). On the contrary, the corresponding aryl iodide gave under these reaction conditions no conversion to the desired triazole **3bd**.

1,5-Disubstituted 1,2,3-triazoles can be prepared highly regioselectively through ruthenium-catalyzed 1,3-dipolar cycloadditions of azides and terminal alkynes.[5] Therefore, we probed our catalytic system in the thermal catalytic direct arylation of triazole **1l** (Scheme 4). This C–H bond functionalization pro-



Scheme 4. Palladium-catalyzed direct arylation of 1,5-disubstituted triazole **1l**.



Scheme 6. Intramolecular palladium-catalyzed direct arylation.

ceeded only sluggishly, which can be explained with a electrophilic substitution-type mechanism.[18a]

This reactivity pattern was reflected by the palladium-catalyzed direct arylation of mono-substituted triazole **1m** (Scheme 5). Hence, 1,5-disubstituted triazole **3bf** was isolated as the major product, along with only small amounts of the fully substituted triazole **3bg**. Furthermore, there was no indication for the formation of the corresponding 1,4-disubstituted triazole by GC/MS analysis of the crude reaction mixture.

Finally, we probed our protocol in a thermal intramolecular direct arylation of a 1,2,3-triazole with a chloride[33] as leaving group (Scheme 6). The excellent catalytic efficacy allowed for an efficient cyclization of substrate **1n**, providing annulated triazole **3bh** in 83% isolated yield.

Conclusions

We have developed a highly active catalyst for *thermal* intermolecular palladium-catalyzed direct arylations of 1,2,3-triazoles with inexpensive aryl *chlorides*. Both *N*-aryl- as well as *N*-alkyl-substituted 1,4-disubstituted 1,2,3-triazoles were converted with high catalytic efficacy to the fully substituted triazoles. Importantly, the catalyst proved broadly applicable, thus, tolerating a variety of important functional groups. Also more challenging electron-rich aryl chlorides were converted efficiently, and an intramolecular direct arylation allowed for the preparation of an annulated triazole. Hence, we have shown that generally applicable direct arylations of 1,2,3-triazoles with aryl chlorides do not require microwave heating and a reaction temperature of 250 °C, but can be achieved at significantly milder reaction temperatures of 105–120 °C.

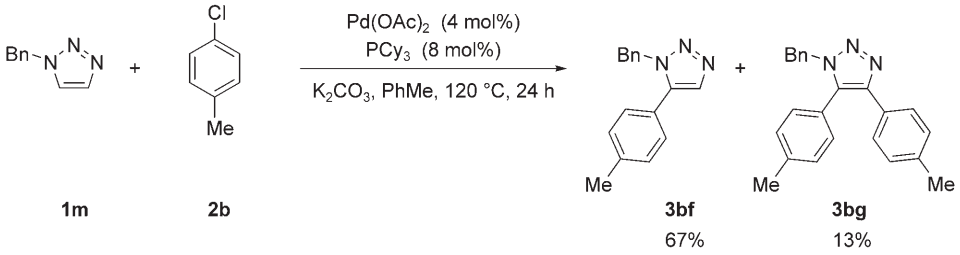
Experimental Section

General Remarks

Catalytic reactions were carried out under an N_2 atmosphere using pre-dried glassware. Triazoles **1** were prepared in analogy to previously described methodologies.[5,34–36] Additional starting materials were obtained from commercial sources, and were used without further purification. Yields refer to isolated compounds, estimated to be >95% pure as determined by ^{1}H NMR and GC. Flash chromatography: Macherey–Nagel silica gel 60 (70–230 mesh). NMR: spectra were recorded on Varian-NMR 300, 500 or 600 instruments in the solvent indicated; chemical shifts (δ) are given in ppm.

Representative Procedure for Palladium-Catalyzed Direct Arylations: Preparation of Triazole 3av (Table 3, entry 9).

A suspension of $Pd(OAc)_2$ (9.0 mg, 4.0 mol%), PCy_3 (22 mg, 8.0 mol%), K_2CO_3 (276 mg, 2.00 mmol), **1i** (215 mg, 1.00 mmol) and **2k** (325 mg, 1.50 mmol) in PhMe (2 mL) was stirred under N_2 for 22 h at 120 °C. Et_2O (75 mL) and H_2O (75 mL) were added to the cold reaction mixture. The separated aqueous phase was extracted with Et_2O (2× 75 mL). The combined organic layers were washed with aqueous NH_4Cl (50 mL), H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated in vacuum. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1) to afford **3av** as a colourless oil; yield: 382 mg (95%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.76–7.69 (m, 4H), 7.60–7.53 (m, 1H), 7.48–7.42 (m, 2H), 7.36–7.29 (m, 1H), 7.24–7.17 (m, 5H), 2.82 (t, $J = 8.0$ Hz,



Scheme 5. Palladium-catalyzed direct arylation of mono-substituted triazole **1m**.

2H), 1.95 (s, 3H), 1.77 (quint, $J=7.9$ Hz, 2H), 1.39 (tq, $J=7.5$, 7.5 Hz, 2H), 0.91 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=195.8$ (C_q), 145.8 (C_q), 137.4 (C_q), 137.0 (C_q), 135.8 (C_q), 135.0 (C_q), 133.9 (C_q), 132.7 (CH), 131.5 (C_q), 131.2 (CH), 130.3 (CH), 130.0 (CH), 129.9 (CH), 128.8 (CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 31.7 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 17.6 (CH_3), 13.8 (CH_3); IR (NaCl): $\nu=2957$, 2860, 1660, 1610, 1498, 1447, 1317, 1177, 996, 939, 924, 857, 766, 668 cm^{-1}; MS (EI): *m/z* (relative intensity) = 395 (3) [M^+], 367 (65), 324 (100), 207 (31), 179 (8), 158 (8), 118 (9), 105 (29), 91 (15), 77 (12), 65 (8); HR-MS (ESI): *m/z* = 396.2072, calcd. for $C_{26}H_{26}N_3O$: 396.2070.

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