

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 substitut-

ed 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.

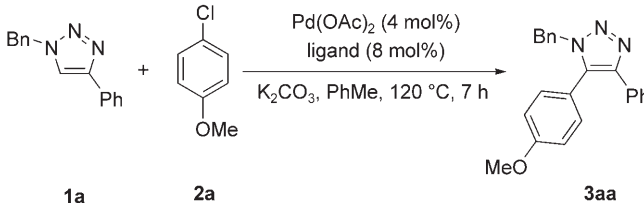
The direct functionalization of C–H bonds^[10–14] in 1,2,3-triazoles could constitute an attractive alternative to traditional cross-couplings with organometallic reagents because of its ecologically and economically

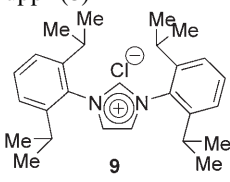
benign nature. Among the known direct arylations of electron-rich heteroarenes, the majority has been accomplished under rhodium or palladium catalyses, applying aryl iodides, bromides, or triflates as electrophiles.^[15–17] Thus, Gevorgyan and co-workers communicated recently on direct arylations of 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

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



Entry	Ligand	Yield
1	-	-
2	PPh_3 (4)	-
3	$P(o-Tol)_3$ (5)	-
4	$P(p-Tol)_3$ (6)	-
5	BINAP (7)	-
6	dppf (8)	-
7	 (9)	-
8	(<i>t</i> -Bu) ₃ PHBF 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.

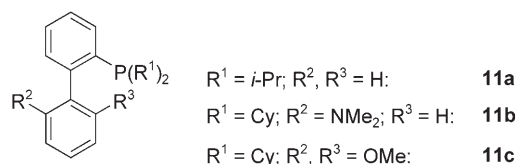


Figure 1. General structure of monophosphine biaryl ligands **11**.

(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.

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]

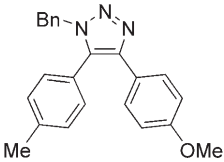
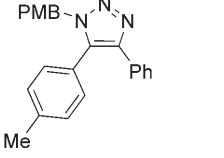
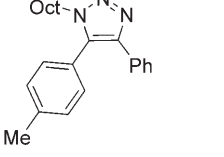
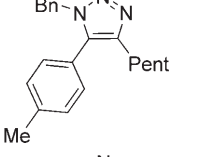
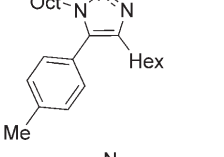
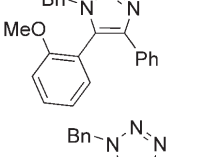
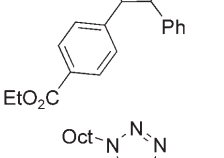
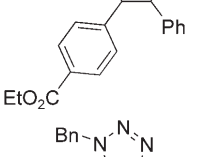
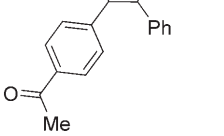
		$ \begin{array}{c} \text{Alk}-\text{N} \begin{array}{c} \diagup \text{N} \diagdown \\ \text{C} \\ \diagdown \text{N} \diagup \end{array} \text{R} \\ \mathbf{1} \end{array} + \text{ArCl} \xrightarrow[\text{K}_2\text{CO}_3, \text{PhMe}, 105 - 120^\circ\text{C}, 18 - 24 \text{ h}]{\text{Pd}(\text{OAc})_2 (4 \text{ mol}\%), \text{PCy}_3 (\mathbf{12}) (8 \text{ mol}\%)} \begin{array}{c} \text{Alk}-\text{N} \begin{array}{c} \diagup \text{N} \diagdown \\ \text{C}(\text{Ar}) \\ \diagdown \text{N} \diagup \end{array} \text{R} \\ \mathbf{3} \end{array} $			
Entry	Alk	R	Ar	Product	Isolated Yield
1	Bn	4-MeOC ₆ H ₄	1b 4-MeC ₆ H ₄	2b 	3ab 74%
2	PMB	Ph	1c 4-MeC ₆ H ₄	2b 	3ac 80%
3	Oct	Ph	1d 4-MeC ₆ H ₄	2b 	3ad 70%
4	Bn	Pent	1e 4-MeC ₆ H ₄	2b 	3ae 66% ^[b]
5	Oct	Hex	1f 4-MeC ₆ H ₄	2b 	3af 68% ^[b]
6	Bn	Ph	1a 2-MeOC ₆ H ₄	2c 	3ag 95%
7	Bn	Ph	1a 4-EtO ₂ CC ₆ H ₄	2d 	3ah 70%
8	Oct	Ph	1d 4-EtO ₂ CC ₆ H ₄	2d 	3ai 63%
9 10 11	Bn	Ph	1a 4-Me(O)CC ₆ H ₄	2e 	(37%) ^[c] 63% ^[d] 67% ^[b]

Table 2. (Continued)

Entry	Alk	R	Ar	Product	Isolated Yield		
12	Bn	Ph	1a	4-NCC ₆ H ₄	2f	3ak	(41%) ^[c]
13							71% ^[b]
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%), K₂CO₃ (1.00–2.00 mmol), PhMe (2 mL), 120 °C, 18–24 h; PMB = 4-MeOC₆H₄CH₂.

^[b] *t*-BuCO₂H (30 mol%).

^[c] GC conversion.

^[d] *t*-BuCO₂H (30 mol%), 1,4-dioxane (2 mL), 105 °C, 18 h.

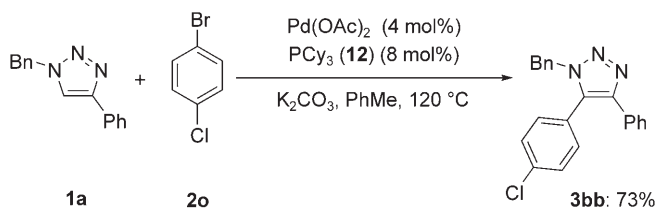
found that heteroaromatic chlorides could be employed in these thermal direct arylation reactions as well. Thus, 3- and even 2-chloropyridine (**2g**, and **2h**) gave rise to triazoles **3al** and **3am**, respectively, in good yields (entries 14 and 15).

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).

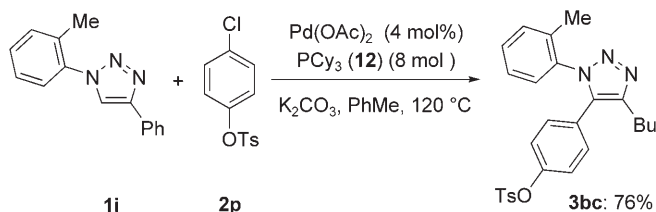
Subsequently, we tested the chemoselectivity of thermal palladium-catalyzed direct arylations of 1,2,3-triazoles within competition experiments. Thus, bromochlorobenzene **2o** reacted highly selectively, giving rise to 1,2,3-triazole **3bb** in good isolated yield through coupling of the aryl bromide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

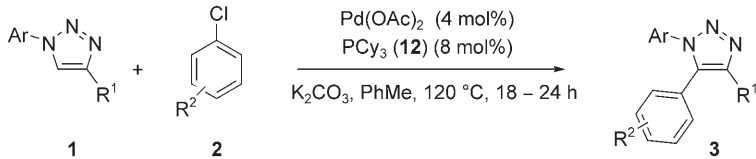
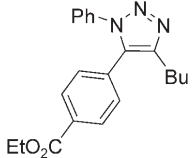
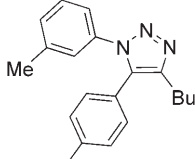
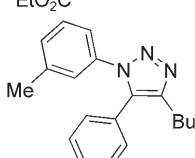
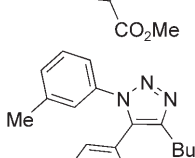
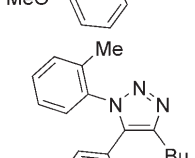
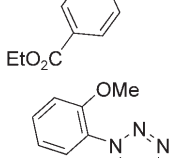
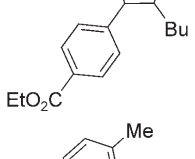
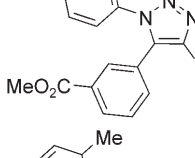
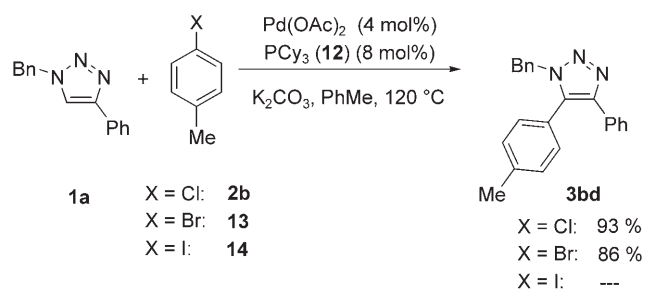
					
Entry	Ar	R ¹	R ²	Product	Isolated Yield
1	Ph	Bu	1g 4-CO ₂ Et	2d 	3an 65%
2	3-MeC ₆ H ₄	Bu	1h 4-CO ₂ Et	2d 	3ao 65%
3	3-MeC ₆ H ₄	Bu	1h 3-CO ₂ Me	2i 	3ap 69%
4	3-MeC ₆ H ₄	Bu	1h 3-OMe	2j 	3aq 60%
5	2-MeC ₆ H ₄	Bu	1i 4-CO ₂ Et	2d 	3ar 68%
6	2-MeOC ₆ H ₄	Bu	1j 4-CO ₂ Et	2d 	3as 62%
7	2-MeC ₆ H ₄	Bu	1i 3-CO ₂ Me	2i 	3at 96%
8	2-MeC ₆ H ₄	CH ₂ TMS	1k 4-CO ₂ Et	2d 	3au 47%

Table 3. (Continued)

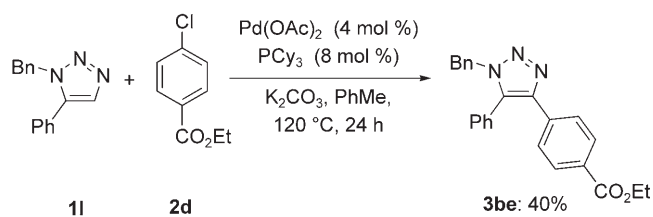
Entry	Ar	R ¹	R ²	Product	Isolated Yield
9	2-MeC ₆ H ₄	Bu	1i 4-C(O)Ph	2k	3av 95%
10	2-MeC ₆ H ₄	Bu	1i 3-C(O)Ph	2l	3aw 80%
11	2-MeC ₆ H ₄	Bu	1i 4-C(O)- <i>t</i> -Bu	2m	3ax 95%
12	2-MeC ₆ H ₄	Bu	1i 4-Me	2b	3ay 70%
13	2-MeC ₆ H ₄	Bu	1i 4-OMe	2a	3az 87%
14	2-MeC ₆ H ₄	Bu	1i 3,5-(OMe) ₂	2n	3ba 90%

[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%), K₂CO₃ (1.00–2.00 mmol), PhMe (2 mL), 120 °C, 18–24 h.

**Scheme 3.** Catalytic direct arylation 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 **11** (Scheme 4). This C–H bond functionalization pro-



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

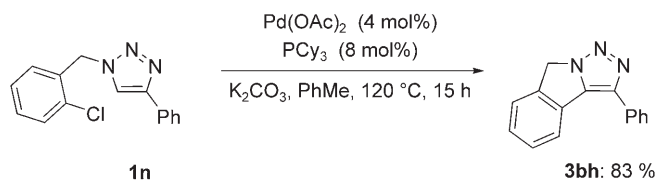
ceeded only sluggishly, which can be explained with a electrophilic substitution-type mechanism.^[18a]

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 re-



Scheme 6. Intramolecular palladium-catalyzed direct arylation.

action temperature of 250 °C, but can be achieved at significantly milder reaction temperatures of 105–120 °C.

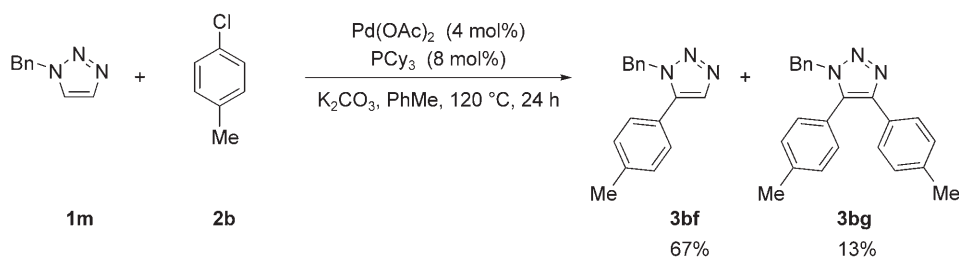
Experimental Section

General Remarks

Catalytic reactions were carried out under an N₂ 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 ¹H 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%), PCy₃ (22 mg, 8.0 mol%), K₂CO₃ (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 N₂ for 22 h at 120 °C. Et₂O (75 mL) and H₂O (75 mL) were added to the cold reaction mixture. The separated aqueous phase was extracted with Et₂O (2 × 75 mL). The combined organic layers were washed with aqueous NH₄Cl (50 mL), H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄ 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%). ¹H NMR (300 MHz, CDCl₃): δ = 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 $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}$: 396.2070.

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