Direct arylations via C−H bond functionalization of 1,2,3-triazoles by reusable Pd/C catalyst in solvent-free conditions

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Abstract: Fully substituted triazoles are synthesized by a sustainable direct arylation reaction performed in solvent-free conditions and in the presence of a recyclable Pd/C heterogeneous catalyst. Exclusion of air as well as anhydrous conditions are not required, enabling a convenient synthesis of 1,4,5-trisubstituted 1,2,3-triazoles and 1,2,3-triazole-fused isoindolines starting from 1,4-disubstituted 1,2,3-triazoles, easily prepared *via* click chemistry, and functionalized aryl iodides.

Introduction

The 1,2,3-triazole ring represents a key structural motif of manifold interest areas including drug discovery,[1] bioconjugation,[2,3] and materials science.[3] These compounds are commonly synthesized by the copper(I)-catalyzed 1,3-dipolar cycloaddition reaction of azides with alkynes (CuAAC), the most prominent example of 'click chemistry', developed by the groups of Sharpless[4] and Meldal.[5] The CuAAC approach is efficient and highly regioselective with terminal alkynes affording 1,4-disubstituted 1,2,3-triazoles in excellent yields.[6] On the contrary, this methodology is found to be not generally useful for the conversion of internal alkynes to fully substituted 1,2,3-triazoles. Among the known methods for the regioselective synthesis of fully substituted 1,2,3-triazoles, the Pd-catalyzed direct arylation of the easy available 1,4-disubstituted 1,2,3-triazoles turns out to be the most general approach.[7] The major drawback of this taste is still represented by the use of toxic solvents (e.g., *N,N*-dimethylformamide, *N*-methyl-2-pyrrolidone, toluene). The use of toxic *N,N*-dimethylformamide also represents a disadvantage for the one-pot multicomponent syntheses of fully decorated triazoles based on use of inexpensive copper catalysts.[8] Only few examples of direct arylation protocols of 1,4-disubstituted 1,2,3-triazoles based on the use of more sustainable experimental conditions have been reported in the literature. For example, protocols for Pd-catalyzed direct arylations in environmentally-benign reaction media, such as polyethylene glycol (PEG)[7d] or biomass-derived γ-valerolactone,[7h,7l] in the presence of reusable palladium catalysts, were developed by Ackermann and co-workers. The development of solvent free conditions would provide much more environmentally benign protocols for direct arylation. In fact, such conditions enable to reduce reaction waste (solvent constitute most of mass wasted in syntheses), avoid the hazards and toxicity associated with some solvents, save energy due to shorter reaction times and simpler workups. A limited number of examples of direct arylation reactions in solvent free conditions have been reported[9] and, to the best of our knowledge, the direct arylation reaction of 1,4-disubstituted 1,2,3-triazoles in solvent free conditions has not been reported in the literature so far. In the frame of our studies on the synthesis of heteroaromatic-based materials[10] as well as on development of innovative Pd-catalyzed methodologies,[11] we report herein the first Pd-catalyzed direct arylation protocol of 1,4-disubstituted 1,2,3-triazoles that is performed in (i) solvent-free, (ii) non-anhydrous conditions, (iii) without exclusion of air, and (iv) in the presence of a reusable catalyst.

Results and Discussion

Our preliminary investigations focused on the direct arylation reaction of **1a**, chosen as a model substrate for the C–H activation, with iodo- or bromobenzene yielding **3a** (Table 1). Initially, we carried out the solvent-free direct arylation reaction of **1a** using $Pd_2(dba)_3$ as the catalyst, Cs_2CO_3 as the base, P(*o*-MeOPh)$_3$ as the ligand and pivalic acid (PivOH) as the additive, in non-

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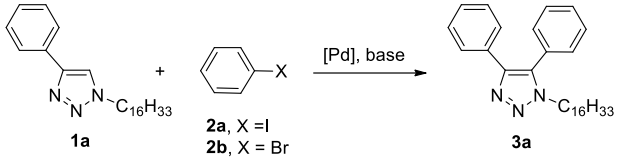
anhydrous conditions and in the presence of air, according to our previously reported conditions for the synthesis of extended heteroaromatic conjugated molecules.[11a] The coupling product **3a** was isolated in high yield (79%, entry 1). Then, with the aim of making the reaction conditions more sustainable, we evaluated the possibility of using only tetra-*n*-butylammonium acetate (Bu_4NOAc) as both the base and the reaction medium, in the absence of any other additive. The effectiveness of using neat Bu_4NOAc as both the base and, together with the reaction by-products Bu_4NBr and CH_3COOH, the reaction medium was recently demonstrated by Kantchev[12] in Ru-catalyzed direct arylation reactions of 2-phenylpyridine and other nitrogen-containing substrates. In neat Bu_4NOAc, a series of commercial Pd complexes were evaluated as pre-catalysts. Moderate yields of **3a** were obtained in the presence of homogeneous catalysts, such as $Pd_2(dba)_3$ (59%, entry 2), $PdCl_2(PPh_3)_2$ (55%, entry 3) and $Pd(OAc)_2$ (54%, entry 4). An increase of the yield of **3a** (70%, entry 5) was obtained in the presence of Pd/C, a recyclable heterogeneous catalyst. Using Pd/C (5 mol %) as the catalyst, we examined the role of the halogen, reaction temperature and catalyst loading. The use of bromobenzene instead of iodobenzene (entry 6) as well as the increase of the reaction temperature (entry 7) drastically reduces the reaction yields. The increase in the catalyst amount from 5 to 10%mol (entry 8) does not produce any enhancement of the reaction yield. A lower catalysts loading (2% mol) causes a decrease in the reaction yield (47% yield *vs* 70%).

Table 1. Optimization of Pd-catalyzed C-H arylations.[a]

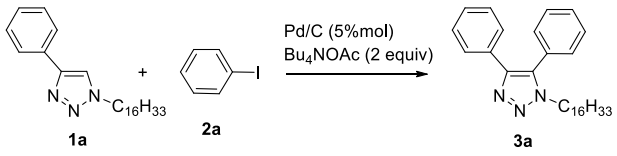


Entry	ArX	catalyst	ligand	additive	base	Temperature (°C)	Yield [b]
1[c]	2a	$Pd_2(dba)_3$	$P(o\text{-}MeOPh)_3$	PivOH	Cs_2CO_3	110	79%
2	2a	$Pd_2(dba)_3$	-	-	Bu_4NOAc	110	59%
3	2a	$PdCl_2(PPh_3)_2$	-	-	Bu_4NOAc	110	55%
4	2a	$Pd(OAc)_2$	-	-	Bu_4NOAc	110	54%
5	2a	Pd/C	-	-	Bu_4NOAc	110	70%
6	2b	Pd/C	-	-	Bu_4NOAc	110	8%
7	2a	Pd/C	-	-	Bu_4NOAc	140	20%
8[d]	2a	Pd/C	-	-	Bu_4NOAc	110	67%
9[e]	2a	Pd/C	-	-	Bu_4NOAc	110	47%

[a] Unless specified, C−H arylation was carried out as follows: **1a** (1 equiv), aryl halide (3 equiv), Pd catalyst (5 mol %), Bu_4NOAc (2 equiv) at 110 °C for 24 h. [b] Yields refer to isolated products. [c] Reaction conditions: **1a** (1 equiv), aryl halide (3 equiv), Pd catalyst (5 mol %), phosphine (10mol %), PivOH (30 mol %), Cs_2CO_3 (2 equiv) at 110 °C for 24 h. [d] Reaction performed in the presence of Pd/C (10 mol %).[e] Reaction performed in the presence of Pd/C (2 mol %).

Although the yields obtained using Pd/C in the presence of neat Bu_4NOAc are slightly lower than those obtained with $Pd_2(dba)_3$ in the presence of Cs_2CO_3, $P(o\text{-}MeOPh)_3$ and pivalic acid (79% *vs* 70%), the use of Pd/C was preferred for subsequent investigations because of more sustainable reaction conditions, including the possibility of catalyst recycle. To probe the catalyst reusability, we recovered the Pd/C by a modified literature protocol[7h] and evaluated the catalytic activity of the recycled material in the subsequent runs (Table 2). We observed an unchanged catalytic activity of the recycled Pd/C until the third run, while a halving of its activity is detected at the fourth run.

Table 2. Reuse of palladium catalyst.[a]



Run	1th	2th	3th	4th[c]
Yield[b]	70%	72%	70%	35%

[a] C−H arylation was carried out as follows: 1a (1 equiv), aryl halide (3 equiv), Pd catalyst (5 mol %), Bu4NOAc (2 equiv) at 110 °C for 24 h. [b] Yields refer to isolated products. [c] After the 4th run, an overall decrease of 27% in catalyst weight is observed.

Having selected Pd/C (5 mol %) in the presence of neat Bu_4NOAc as the reaction system of choice for this study, we investigated the substrate versatility reacting the 1,2,3-triazoles **1a-d**, bearing a different ring substitution pattern, with various aryl iodides. The results of this screening are shown in the Scheme 1.

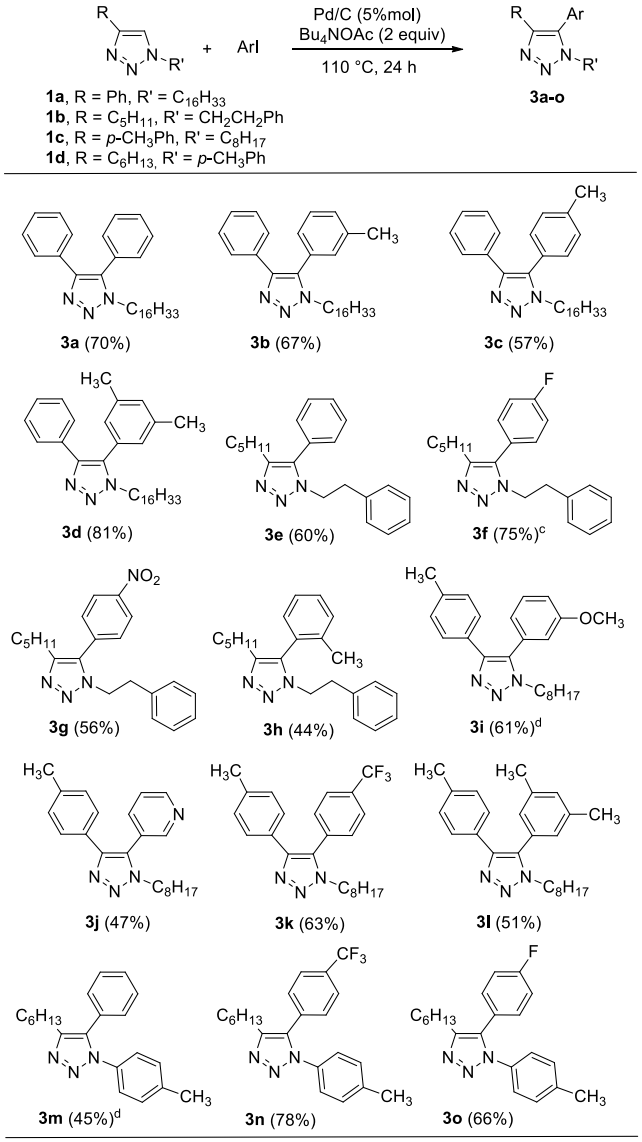
The triazole-aryl coupling reactions occurred in moderate to good yields using aryl iodides functionalized with electron-donating functionalities, such as methyl (**3b**: 67%, **3c**: 57%, **3d**: 81%, **3h**: 44%, **3l**: 51%) and methoxy (**3i**: 61%) groups.The yield obtained with 2-iodotoluene (**3h**: 44%), which is lower with respect to those obtained with meta and para methyl substituted iodides, suggests that the reaction may be affected by steric effects. The triazole-aryl coupling reactions also occurred in good yields using aryl iodides functionalized with electron-withdrawing groups, such as fluorine (**3f**: 61%, **3o**: 66%), nitro (**3g**: 56%) and trifluoromethyl (**3k**: 63%, **3n**: 78%) groups, and pyridyl iodides (**3j**: 47%), while yields lower than 30% were obtained with aryl iodides bearing ketone and ester groups. No effective chemoselectivity was

observed in the reaction between triazole **1b** and 3-iodobromobenzene. The low or moderate yields sometimes observed in triazole-aryl coupling reactions performed with our protocol are mainly due to a low conversion of the starting triazole and only minimally to the formation of by-products. A different ring substitution pattern does not seem to influence the triazole-aryl coupling reactions course since they runned both with N-alkyl (**3a-l**) and with N-aryl (**3m-o**) triazoles. Our strategy was also proved viable for the intramolecular C–H functionalization with substrates **4a-b** leading to 1,2,3-triazole-fused isoindolines **5a-b**.[7l] A good yield was obtained in the presence of Pd/C (5 mol %) and neat Bu_4NOAc (4 equiv) at 120°C for 48h (Scheme 2).

Conclusions

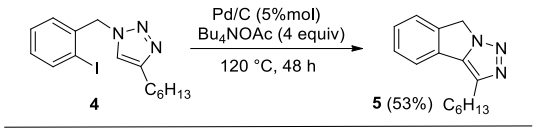
In conclusion, we have reported here the first example of direct arylation reaction of 1,4-disubstituted 1,2,3-triazoles in solvent free conditions that allow both to reduce reaction waste and to avoid the hazards and toxicity associated with some solvents. Moreover, the use of Pd/C, a recyclable heterogeneous catalyst, in non-anhydrous conditions and in presence of air, causes our protocol to be an environmentally attractive procedure for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles and 1,2,3-triazole-fused isoindolines. Despite the solvent free conditions represent an undoubted advantage of our methodology, further effort will have to be made to reduce or eliminate the use of organic solvents in the product isolation (no workup is required in our conditions), so increasing the protocol eco-sustainability.

Scheme 1. Synthesis of compounds **3a-o**[a,b]



[a]Unless specified, C−H arylation was carried out as follows: **1a-d** (1 equiv), aryl iodide (3 equiv), Pd/C (5 mol %), Bu_4NOAc (2 equiv) at 110 °C for 24 h. [b]Yields refer to isolated products. [c]Reaction performed on a 1-mmol scale of **1b**. [d]Yield from NMR data.

Scheme 2. Synthesis of compounds **5**[a,b]



[a] C−H arylation was carried out as follows: **4** (1 equiv), Pd/C (5 mol %), Bu_4NOAc (4 equiv) at 120 °C for 48 h. [b] Yield refers to isolated product.

Experimental Section

General remarks: Reagents were purchased at the highest commercial quality from Sigma-Aldrich and used without further purification. 4-Hexyl-

1-(*p*-tolyl)-1*H*-1,2,3-triazole **1d**[13] was synthesized according to literature procedures. Unless specified, preparative column chromatography was carried out using Macherey-Nagel silica gel (60, particle size 0.063-0.2 mm). Macherey-Nagel aluminum sheets with silica gel 60 F254 were used for TLC analyses. All new com-pounds were characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR and LC-MS analysis. ^{1}H-NMR and ^{13}C-NMR spectra were were acquired on an Agilent 500 spectrometer at 500 and at 126 MHz, respectively, using the $CDCl_3$ residual proton peak at δ = 7.26 ppm as internal standard for ^{1}H spectra and the signals of $CDCl_3$ at δ = 77.16 ppm as internal standard for ^{13}C spectra. High-resolution mass spectra were acquired with a Shimadzu high-performance liquid chromatography ion trap time-of flight (LC-IT-TOF) mass spectrometer via direct infusion of the samples (elution with 0.1% (v/v) formic acid in methanol). Melting points were determined on a Stuart Scientific Melting point apparatus SMP3.

Synthesis of triazoles 1a-d and 4.

*1-Hexadecyl-4-phenyl-1H-1,2,3-triazole (**1a**).* Phenyl acetylene (0.78 g, 7.64 mmol) and hexadecylazide (1.65 g, 6.37mmol) were added at room temperature to a solution of $Cu(OAc)_2{\cdot}H_2O$ (0.25g, 1.27 mmol) in H_2O (50 mL) in a capped flask. The reaction mixture was warmed at 100°C and stirred at the same temperature for 5h. After cooling at room temperature, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The organic extracts were washed with an aqueous solution of brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 9:1) affording 1.85 g of compound **1a** (79% yield) as a white solid. mp = 100-101 °C (after crystallization from CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.6 Hz, 2H), 7.41 (s, 1H), 7.42 (t like, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 4.38 (t, *J* = 7.2 Hz, 2H), 1.98-1.90 (m, 2H), 1.37-1.21 (m, 26H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.9, 130.9, 128.9, 128.2, 125.8, 119.5, 50.6, 32.1, 30.5, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.5, 29.1, 26.6, 22.8, 14.3; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{40}N_3$ 370.3217; Found 370.3195.

*4-Pentyl-1-phenethyl-1H-1,2,3-triazole (**1b**).* 1-Heptyne (0.55 g, 5.71 mmol) and 2-phenyethylazide (0.700 g, 4.76 mmol) were added at room temperature to a solution of $Cu(OAc)_2{\cdot}H_2O$ (0.19g, 0.95 mmol) in H_2O (20 mL) in a capped flask. The reaction mixture was warmed at 100°C and stirred at the same temperature for 6h. After cooling at room temperature, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The organic extracts were washed with an aqueous solution of brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 7:3) affording 1.01 g of compound **1b** (87 % yield) as a whitish low-melting solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21-7.11 (m, 3H), 6.99 (d, *J* = 7.2 Hz, 2H), 6.98 (s, 1H), 4.43 (t, *J* = 7.3 Hz, 2H), 3.08 (t, *J* = 7.3 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.57-1.50 (m, 2H), 1.29-1.17 (m, 4H), 0.81 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.7, 137.1, 128.4, 126.7, 120.9, 51.1, 36.6, 31.1, 28.9, 25.3, 22.2, 13.8; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{22}N_3$ 244.1808; Found 244.1796.

*1-Octyl-4-(p-tolyl)-1H-1,2,3-triazole (**1c**).* 1-Ethynyl-4-methylbenzene (0.342 g, 2.95 mmol) and octylazide (0.381 g, 2.45 mmol) were added at room temperature to a solution of $Cu(OAc)_2{\cdot}H_2O$ (0.098 g, 0.49 mmol) in H_2O (15 mL) in a capped flask. The reaction mixture was warmed at 100°C and stirred at the same temperature for 5h. After cooling at room temperature, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The organic extracts were washed with an aqueous solution of brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 7:3) affording 0.604 g of compound **1c** (91% yield) as a white solid. mp = 75-76°C (after washing with hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.9 Hz, 2H), 7.71 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 4.38 (t, *J* = 7.3 Hz, 2H), 2.38 (s, 3H), 1.97-1.90 (m, 2H), 1.39-1.22 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.9, 138.0, 129.6, 128.0, 125.7, 119.2, 50.6, 31.8, 30.5, 29.2, 29.1, 26.7, 22.7, 21.4, 14.2; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{26}N_3$ 272.2121; Found 272.2102.

*4-Hexyl-1-(p-tolyl)-1H-1,2,3-triazole (**1d**).*[13,14] Compound **1d** was synthesized from *p*-tolylboronic acid (408 mg, 3 mmol), NaN_3 (234 mg, 3.6 mmol) and 1-octyne (364 mg, 3.3 mmol) in accordance with a literature procedure (201 mg, 28% yield).[13] Spectroscopic data are in agreement with those previously reported in the literature.[14]

*4-Hexyl-1-(2-iodobenzyl)-1H-1,2,3-triazole (**4**).* 2-Iodobenzylazide (0.700 g, 2.70 mmol) and 1-octyne (0.356 g, 3.24 mmol) were added at room temperature to a solution of $Cu(OAc)_2{\cdot}H_2O$ (0.108 g, 0.54 mmol) in H_2O (15 mL) in a capped flask. The reaction mixture was warmed at 100°C and stirred at the same temperature for 2h. After cooling at room temperature, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The organic extracts were washed with an aqueous solution of brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexane:ethyl acetate = 7:3) affording 0.775 g of compound **4** (78% yield) as a white solid, mp = 65-66°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.32 (td, *J* = 7.6, 1.1 Hz, 1H), 7.28 (br s, 1H), 7.06-7.01 (m, 2H), 5.58 (s, 2H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.69-1.61 (m, 2H), 1.38-1.25 (m, 6H), 0.87 (t, *J* = ,7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.1, 139.9, 137.9, 130.4, 129.6, 129.1, 121.0, 98.6, 58.4, 31.7, 29.5, 29.0, 25.9, 22.7, 14.2; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}N_3I$ 370.0775; Found 370.0752.

Synthesis of triazoles 3a-o.

General Procedure: A round-bottom flask (10 mL) with a screw cap and equipped with a magnetic stirrer was charged with 1,2,3-triazole (1 equiv), aryl iodide (3 equiv), Pd/C (5% mol) and Bu_4NOAc (2 equiv). The resulting heterogeneous reaction mixture was reacted at 110 °C (sand bath) under magnetic stirring. After 24 h, the mixture was cooled to room temperature, diluted with ethyl acetate and the resulting suspension was centrifuged to recover both the heterogeneous catalyst as a solid material and the organic layer containing the crude product (2 times). The organic extracts were concentrated under vacuum and the crude product was purified by column chromatography on silica gel. **Procedure for recovery of Pd/C**: to the solid material recovered by centrifugation, EtOH was added. The resulting suspension was stirred for 10 min and the solvent was removed after centrifugation (2 times). The residual Pd/C was dried in vacuum at 60 °C overnight and used for the subsequent run.

*1-Hexadecyl-4,5-diphenyl-1H-1,2,3-triazole (**3a**).* Compound **3a** was synthesized from **1a** (50 mg, 0.14 mmol) and iodobenzene (86 mg, 0.42 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 9:1) afforded compound **3a** (44 mg, 70% yield) as a white solid, mp = 63-64°C (after crystallization from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.53-7.49 (m, 3H), 7.34-7.31 (m, 2H), 7.28-7.21 (m, 3H), 4.19 (t, *J* = 7.2 Hz, 2H), 1.82-1.74 (m, 2H), 1.28-1.17 (m, 26H), 0.88 (t, *J* = 6.9 Hz, 3H) ; ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.3, 133.8, 131.2, 130.1, 129.7, 129.5, 128.5, 128.4, 127.7, 126.9, 48.4, 32.1, 30.2, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.0, 26.5, 22.8, 14.3; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{44}N_3$ 446.3530; Found 446.3529.

*1-Hexadecyl-4-phenyl-5-(m-tolyl)-1H-1,2,3-triazole (**3b**).* Compound **3b** was synthesized from **1a** (50 mg, 0.14 mmol) and 1-iodo-3-methylbenzene (92 mg, 0.42 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 8.5:1.5) afforded compound **3b** (43 mg, 67% yield) as a white solid, mp = 66-67°C (after crystallization from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.54 (m, 2H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.32 (d *J* = 7.7 Hz, 1H), 7.28-7.21 (m, 3H), 7.14-7.10 (m, 2H), 4.18 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 1.82-1.75 (m, 2H), 1.32-1.16 (m, 26H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.1, 139.3, 133.9, 131.3, 130.6, 130.5, 129.3, 128.5, 128.4, 127.6, 127.2, 126.8, 48.4, 32.1, 30.2, 29.8, 29.8, 29.7, 29.5, 29.5, 29.0, 26.5, 22.8, 21.6, 14.3; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{46}N_3$ 460.3686; Found 460.3691.

*1-Hexadecyl-4-phenyl-5-(p-tolyl)-1H-1,2,3-triazole (**3c**).* Compound **3c** was synthesized from **1a** (50 mg, 0.14 mmol) and 1-iodo-4-methylbenzene (92 mg, 0.42 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 8.5:1.5) afforded compound **3c** (37 mg, 57% yield) as a white solid, mp = 54-55°C (after crystallization from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.28-7.21 (m, 3H), 7.20 (d, *J* = 7.9 Hz, 2H), 4.18 (t, *J* = 7.4 Hz, 2H), 2.45 (s, 3H), 1.81-1.74 (m, 2H), 1.32-1.17 (m, 26H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.0, 139.6, 133.7, 131.2, 130.0, 129.8, 128.3, 127.5, 126.7, 125.1, 48.2, 31.9, 30.1, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 29.3, 28.9, 26.4, 22.7, 21.4, 14.1; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{46}N_3$ 460.3686; Found 460.3692.

*5-(3,5-Dimethylphenyl)-1-hexadecyl-4-phenyl-1H-1,2,3-triazole (**3d**).* Compound **3d** was synthesized from **1a** (50 mg, 0.14 mmol) and 1-iodo-3,5-dimethylbenzene (98 mg, 0.42 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 8.5:1.5) afforded compound **3d** (54 mg, 81% yield) as a white solid, mp = 69-70°C (after crystallization from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59-7.56 (m, 2H), 7.28-7.20 (m, 3H), 7.13 (br s, 1H), 6.92 (br s, 2H), 4.16 (t, *J* = 7.4 Hz, 2H), 2.36 (s, 6H), 1.82-1.75 (m, 2H), 1.32-1.17 (m, 26H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.0, 139.1, 134.1, 131.4, 131.4, 128.5, 128.3, 127.7, 127.6, 126.7, 48.3, 32.1, 30.2, 29.8, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 29.0, 26.5, 22.8, 21.4, 14.3; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{48}N_3$ 474.3843; Found 474.3839.

*4-Pentyl-1-phenethyl-5-phenyl-1H-1,2,3-triazole (**3e**).* Compound **3e** was synthesized from **1b** (50 mg, 0.21 mmol) and iodobenzene (129 mg, 0.63 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 8.5:1.5) afforded compound **3e** (40 mg, 60% yield) as a viscous dark yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.37 (m, 3H), 7.21-7.18 (m, 3H), 6.95-6.92 (m, 2H), 6.92-6.88 (m, 2H), 4.38 (t, *J* = 7.3 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.56 (t, *J* = 7.8 Hz, 2H), 1.64-1.56 (m, 2H), 1.28-1.18 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.7, 137.5, 134.7, 129.7, 129.2, 128.9, 128.9, 128.7, 127.8, 126.9, 49.5, 36.8, 31.5, 29.4, 25.0, 22.5, 14.1; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{26}N_3$ 320.2121; Found 320.2121.

*5-(4-Fluorophenyl)-4-pentyl-1-phenethyl-1H-1,2,3-triazole (**3f**).* Compound **3f** was synthesized from **1b** (243 mg, 1.00 mmol) and 1-fluoro-4-iodobenzene (666 mg, 3 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:diethyl ether: dichloromethane = 4:3:3) afforded compound **3f** (254 mg, 75% yield) as a viscous pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22-7.18 (m, 3H), 7.09-7.04 (m, 2H), 6.89-6.85 (m, 2H), 6.82-6.78 (m, 2H), 4.35 (t, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 7.1 Hz, 2H), 2.54 (t, *J* = 7.8 Hz, 2H), 1.62-1.54 (m, 2H), 1.27-1.16 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H) ; ^{13}C NMR (126 MHz, $CDCl_3$): δ 163.2 (d, *J* = 250.7 Hz), 145.5, 137.3, 134.2, 131.7 (d, *J* = 8.7 Hz), 128.9 (d, *J* = 15.9 Hz), 127.1, 123.4, 116.2 (d, *J* = 21.8 Hz); HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{25}FN_3$ 338.2027; Found 338.2020.

*5-(4-Nitrophenyl)-4-pentyl-1-phenethyl-1H-1,2,3-triazole (**3g**).* Compound **3g** was synthesized from **1b** (50 mg, 0.21 mmol) and 1-iodo-4-nitrobenzene (153 mg, 0.63 mmol) in accordance with the general procedure. Purification by column chromatography (silica gel, particle size 0.040-0.063 mm, from hexane:diethyl ether:dichloromethane = 4:1:5 to hexane: ethyl acetate 7:3) afforded compound **3g** (42 mg, 56% yield) as a viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.1 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 7.0 Hz, 2H) 4.39 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 6.6 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.63-1.55 (m, 2H), 1.28-1.16 (m, 4H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.1, 146.1, 137.2, 134.3, 133.1, 130.7, 130.0, 128.9, 127.2, 124.0, 50.0, 36.9, 31.4, 29.4, 25.0, 22.4, 14.1; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{25}N_4O_2$ 365.1972; Found 365.1957.

*4-Pentyl-1-phenethyl-5-(o-tolyl)-1H-1,2,3-triazole (**3h**).* Compound **3h** was synthesized from **1b** (50 mg, 0.21 mmol) and 1-iodo-2-methylbenzene (137 mg, 0.63 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 3:2) afforded compound **3h** (31 mg, 44% yield) as a viscous yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23-7.16 (m, 4H), 6.89 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.65 (d, *J* = 7.6 Hz, 1H), 4.37 (ddd, *J* = 13.7, 8.5, 5.6 Hz, 1H), 4.05 (dt, *J* = 13.7, 7.9 Hz, 1H), 3.14 (dt, *J* = 13.7, 7.9 Hz, 1H), 3.05 (ddd, *J* = 13.7, 8.5, 5.6 Hz, 1H), 2.55 (td, *J* = 14.9, 7.6 Hz, 1H), 2.41 (td, *J* = 14.9, 7.6 Hz, 1H), 1.95 (s, 3H), 1.62-1.51 (m, 2H), 1.25- 1.17 (m, 4H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.6, 138.0, 137.4, 134.1, 130.8, 130.5, 129.9, 128.9, 128.8, 127.0, 126.8, 126.2, 49.5, 36.6, 31.5, 29.0, 25.1, 22.4, 19.5, 14.1; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{28}N_3$ 334.2278; Found 334.2266.

*5-(3-Methoxyphenyl)-1-octyl-4-(p-tolyl)-1H-1,2,3-triazole (**3i**).* Compound **3i** was synthesized from **1c** (50 mg, 0.18 mmol) and 1-iodo-3-methoxybenzene (129 mg, 0.55 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 8.5:1.5) afforded compound **3j** and unreacted **1c** as an inseparable mixture (2:1 ratio, 61% yield by NMR data). HRMS (LC-IT-TOF) m/z: [M+H]+ Calcd for $C_{24}H_{32}N_3O$ 378.2540; Found 378.2523.

*3-(1-octyl-4-(p-tolyl)-1H-1,2,3-triazol-5-yl)pyridine (**3j**).* Compound **3j** was synthesized from **1c** (50 mg, 0.18 mmol) and 3-iodopyridine (113 mg, 0.55 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 8.5:1.5) afforded compound **3j** (30 mg, 47% yield) as a viscous brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$):□□□8.78 (br d, *J* = 3.5 Hz, 1H), 8.63 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.21 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 1.83-1.75 (m, 2H), 1.28-1.17 (m, 10H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 150.0, 145.6, 138.3, 138.1, 129.8, 129.5, 127.5, 127.0, 125.3, 124.3, 48.7, 31.8, 30.3, 29.1, 29.0, 26.6, 22.7, 21.3, 14.2; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{29}N_4$ 349.2387; Found 349.2368.

*1-Octyl-4-(p-tolyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole (**3k**).* Compound **3k** was synthesized from **1c** (50 mg, 0.18 mmol) and 1-iodo-4-(trifluoromethyl)benzene (150 mg, 0.55 mmol) in accordance with the general procedure. Purification by column chromatography (silica gel, particle size 0.040-0.063 mm, hexane:ethyl acetate = 8:2) afforded compound **3k** (47 mg, 63% yield) as a viscous colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H),7.37 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.20 (t, *J* = 7.3 Hz, 2H), 2.32 (s,3H), 1.82-1.74 (m, 2H), 1.27-1.16 (m, 10H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.9, 137.9, 132.5, 132.0, 131.8 (q, *J* = 33.2 Hz), 130.6, 129.4, 127.8, 127.0, 126.4 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 272.5 Hz), 48.6, 31.8, 30.3, 29.1, 29.0, 26.5, 22.7, 21.3, 14.2; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{29}F_3N_3$ 416.2308; Found 416.2307.

5-(3,5-Dimethylphenyl)-1-octyl-4-(p-tolyl)-1H-1,2,3-triazole ***(3l)***. Compound **3l** was synthesized from **1c** (50 mg, 0.18 mmol) and 1-iodo-3,5-dimethylbenzene (127 mg, 0.55 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 4:1) afforded compound **3l** (35 mg, 51% yield) as a white solid, mp = 77-78 °C (after crystallization from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.1 Hz, 2H), 7.13 (br s, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.92 (br s, 2H), 4.15 (t, *J* = 7.5 Hz, 2H), 2.35 (s, 6H), 2.31 (s, 3H), 1.82-1.74 (m, 2H), 1.28-1.17 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.0, 139.0, 137.3, 133.7, 131.3, 129.2, 128.6, 128.4, 127.7, 126.6, 48.2, 31.8, 30.2, 29.1, 29.0, 26.5, 22.7, 21.4, 21.3, 14.2; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{34}N_3$ 376.2747; Found 376.2726.

4-Hexyl-5-phenyl-1-(p-tolyl)-1H-1,2,3-triazole ***(3m)***. Compound **3m** was synthesized from **1d** (50 mg, 0.21 mmol) and iodobenzene (127 mg, 0.62 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate = 7.5:2.5) afforded compound **3m** and unreacted **1d** as an inseparable mixture (1.5:1 ratio, 45% yield by NMR data); HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{26}N_3$ 320.2121; Found 320.2106.

4-Hexyl-1-(p-tolyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole ***(3n)***. Compound **3n** was synthesized from **1d** (50 mg, 0.21 mmol) and 1-iodo-4-(trifluoromethyl)benzene (168 mg, 0.62 mmol) in accordance with the general procedure. Purification by column chromatography (hexane:ethyl acetate:diethy ether = 8:1:1) afforded compound **3n** (63 mg, 78% yield) as a viscous pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.38 (s, 3H), 1.77-1.69 (m, 2H), 1.37-1.30 (m, 2H), 1.29-1.23 (m, 4H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.6, 139.2, 134.0, 132.3, 131.6, 130.8 (q, *J* = 32.8 Hz), 129.9, 129.9, 125.7 (q, *J* = 3.7 Hz), 124.7, 123.7 (q, *J* = 272.2 Hz), 31.5, 29.6, 29.0, 25.1, 22.5, 21.1, 14.0; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{25}F_3N_3$ 388.1995; Found 388.1983.

5-(4-Fluorophenyl)-4-hexyl-1-(p-tolyl)-1H-1,2,3-triazole ***(3o)***. Compound **3o** was synthesized from **1d** (50 mg, 0.21 mmol) and 1-fluoro-4-iodobenzene (138 mg, 0.62 mmol) in accordance with the general procedure. Purification by column chromatography (silica gel, particle size 0.040-0.063 mm, hexane:ethyl acetate:diethy ether = 8:1:1) afforded compound **3o** (46 mg, 66% yield) as a white solid, mp = 94-95°C (after crystallization from hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20-7.04 (m, 8H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.36 (s, 3H), 1.75-1.67 (m, 2H), 1.36-1.22 (m, 6H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 162.9 (d, *J* = 249.6 Hz), 164.3, 139.0, 134.4, 133.0, 131.6 (d, *J* = 8.3 Hz), 129.9, 124.8, 124.0 (d, *J* = 3.5 Hz), 116.2 (d, *J* = 21.9 Hz), 31.6, 29.7, 29.2, 25.3, 22.7, 21.3, 14.2; HRMS (LC-IT-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{25}FN_3$ 338.2027; Found 338.2009.

Synthesis of *3-hexyl-8H-[1,2,3]triazolo[5,1-a]isoindole* (5).[7l]

A round-bottom flask (10 mL) with a screw cap and equipped with a magnetic stirrer was charged with **4** (100 mg, 0.27 mmol), Pd/C (5% mol) and Bu_4NOAc (4 equiv). The resulting heterogeneous reaction mixture was reacted at 120 °C (sand bath) under magnetic stirring. After 48 h, the mixture was cooled to room temperature and the crude was purified by column chromatography (silica gel, particle size 0.040-0.063 mm, hexane:ethyl acetate = 7:3) afforded compound **5** (35 mg, 53% yield) as a pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 5.30 (s, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 1.85-1.77 (m, 2H), 1.46-1.39 (m, 2H), 1.38-1.26 (m, 4H), 0.88 (7, *J* = 7.0 Hz, 3H).[7l]

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Keywords: C-H activation • solvent-free reactions • Pd-catalysis • 1,2,3-triazoles • nitrogen-based heterocycles

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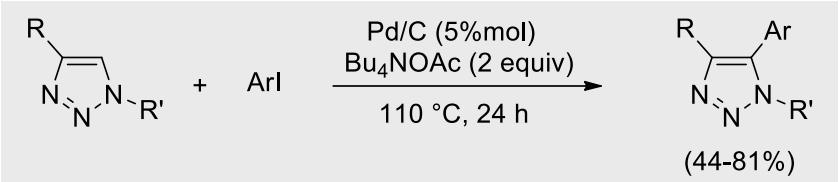
Entry for the Table of Contents

FULL PAPER



1,4,5-Trisubstituted 1,2,3-triazoles and 1,2,3-triazole-fused isoindolines are synthesized by a sustainable Pd-catalyzed direct arylation reaction performed in solvent-free conditions and in the presence of a recyclable heterogeneous catalyst.

Heterogeneous Pd-catalysis, solvent-free conditions

*Angela Punzi, Nicola Zappimbulso, Gianluca M. Farinola**

Page No. – Page No.

Direct arylations via C−H bond functionalization of 1,2,3-triazoles by reusable Pd/C catalyst in solvent-free conditions