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Microwave-Assisted Palladium-Catalyzed Direct Arylation of 1,4-Disubstituted 1,2,3-Triazoles with Aryl Chlorides

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Abstract: Treatment of 1,4-disubstituted 1,2,3-triazoles with aryl chlorides in the presence of potassium carbonate under palladium catalysis and microwave irradiation at 250 °C for 15 min leads to arylation of the triazole at the 5-position. A variety of functional groups, including ester and hydroxy groups, are compatible. The procedure is suitable for the regioselective preparation of trisubstituted triazoles. Microwave irradiation accelerates the reaction, thus allowing the rapid synthesis of trisubstituted triazoles, which are difficult to synthesize selectively.

Keywords: arylation · C–C coupling · nitrogen heterocycles · palladium · triazoles

Introduction

1,2,3-Triazoles are often found in biologically active compounds; hence, they are important heterocycles in medicinal as well as organic chemistry. One of the representative methods for the synthesis of 1,2,3-triazoles is the reaction of alkynes with organic azides. Highly regioselective syntheses of 1,4- and 1,5-disubstituted triazoles have been established by using copper[1] and ruthenium[2] catalysts, respectively. However, transition-metal-catalyzed as well as thermal coupling reactions of internal alkynes with organic azides lack regioselectivity and/or generality.[2,3] Little is known about the regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles. An alternative approach to such trisubstituted triazoles is the use of metalated triazoles. The reaction of magnesium acetylides with organic azides provides 1,5-disubstituted 4-magnesio-1,2,3-triazoles, which can react further with various electrophiles.[4] However, this approach is limited because of the high reactivity of the magnesium species.

Transition-metal-catalyzed direct arylation reactions of aromatic compounds with aryl halides have attracted increasing attention.[5] Taking advantage of the ready availability of 1,4-disubstituted triazoles by the copper-catalyzed reaction,[1] we report herein the palladium-catalyzed direct arylation of 1,4-disubstituted triazoles with aryl chlorides. The arylation takes place at the 5-position and represents a regioselective access to 1,4,5-trisubstituted triazoles. The combined use of tricyclohexylphosphine as the ligand and microwave heating[6] at 250 °C allowed us to employ aryl chlorides as arylating agents[7] and to complete the reaction within only 15 min. Gevorgyan and co-workers[8] independently reported similar arylation reactions, but these reactions required aryl bromides and a prolonged reaction time of 24 h. One palladium-catalyzed direct arylation of a 1,2,4-triazole with an aryl chloride was reported,[9] although the reaction took 24 h to complete.

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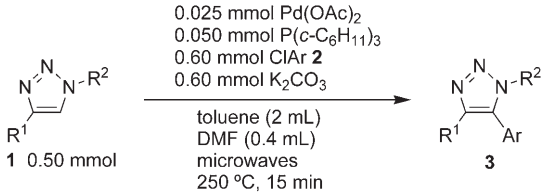
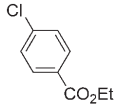
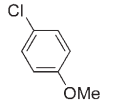
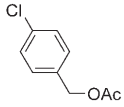
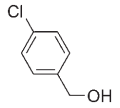
Results and Discussion

A mixture of 1-benzyl-4-phenyl-1,2,3-triazole (**1a**) and *o*-chlorotoluene (**2a**) was heated in toluene/DMF at 250 °C under microwave irradiation for 15 min in the presence of potassium carbonate and $Pd(OAc)_2/P(c\text{-}C_6H_{11})_3$ catalyst. Extractive workup followed by chromatographic purification provided the corresponding arylated product **3aa** in 99% yield (Table 1, entry 1).

Various combinations of aryl chlorides and triazoles were subjected to the palladium-catalyzed reaction. Aryl chlorides with an electron-withdrawing or -donating group reacted smoothly (Table 1, entries 2 and 3). The ester functionality is compatible under the reaction conditions (Table 1, entries 2 and 4). The phenylation reaction of **1a** proceeded in the presence of only 0.5 mol% of $Pd(OAc)_2$ (Table 1, entry 5). A decrease in the amount of catalyst led to incomplete conversion (Table 1, entry 6). Conversions of sterically

Table 1. Pd-catalyzed arylation of 1,4-disubstituted 1,2,3-triazoles with aryl chlorides under microwave irradiation.



Entry	1	R^1	R^2	2	3	Yield [%]
1	**1a**	Ph	Bn		**2a**	**3aa**	99
2	**1a**				**2b**	**3ab**	84
3	**1a**				**2c**	**3ac**	90
4	**1a**				**2d**	**3ad**	77
5[a]	**1a**				**2e**	**3ae**	98
6[b,c]	**1a**			**2e**		**3ae**	40
7[c,d]	**1a**				**2f**	**3af**	81
8[c,d]	**1a**				**2g**	**3ag**	88
9[e]	**1b**	n-C_6H_{13}	Bn	**2a**		**3ba**	93
10[f]	**1b**			**2b**		**3bb**	86
11[d]	**1b**			**2c**		**3bc**	90
12[d]	**1b**			**2d**		**3bd**	91
13	**1b**			**2e**		**3be**	88
14	**1b**				**2h**	**3bh**	–
15	**1c**	4-pyridyl	Bn	**2e**		**3ce**	89
16	**1d**		Bn	**2e**		**3de**	77
17	**1e**	Ph	4-tol	**2e**		**3ee**	100

[a] 0.0025 mmol of $Pd(OAc)_2$ and 0.0050 mmol of $P(c\text{-}C_6H_{11})_3$ were used. [b] 0.00025 mmol of $Pd(OAc)_2$ and 0.00050 mmol of $P(c\text{-}C_6H_{11})_3$ were used. [c] Performed for 2 h. [d] Aryl chloride **2** (1.0 mmol) and K_2CO_3 (1.0 mmol) were used. [e] Performed for 30 min. [f] Performed for 20 min. Bn = benzyl, DMF = *N*,*N*-dimethylformamide, tol = tolyl.

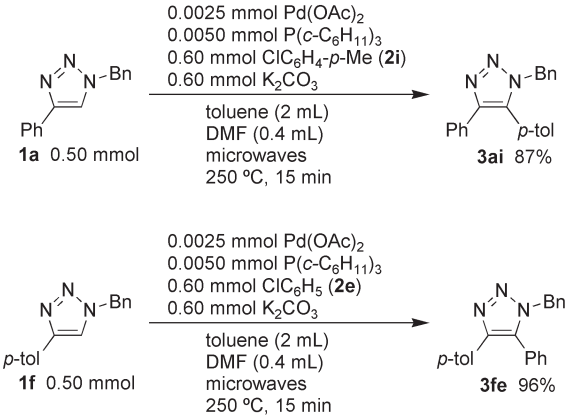
Abstract in Japanese:

炭酸カリウムと触媒量の酢酸パラジウムならびにトリシクロヘキシルホスフィン存在下 1,4-二置換 1,2,3-トリアゾールと塩化アリールの混合物をトルエン/ DMF 混合溶媒中マイクロ波照射により 250°C に加熱するとトリアゾールの 5 位でアリール化反応が進行する。反応はわずか 15 分で完結するため、1,4,5-三置換トリアゾールの選択的かつ迅速な合成法として有用である。

demanding aryl chlorides **2f** and **2g** were slow; they required 2 h for completion (Table 1, entries 7 and 8).

Besides **1a**, hexyl-substituted **1b** also participated in the reaction, albeit with slightly lower efficiency (Table 1, entries 9–13). The arylation reactions with **2a** and **2b** did not proceed to completion within 15 min, and longer reaction times were necessary (Table 1, entries 9 and 10). In other cases, larger amounts of potassium carbonate and aryl chlorides were essential to attain high yields (Table 1, entries 11 and 12). The phenylation of **1b** was less efficient than that of **1a**: 5 mol% of $Pd(OAc)_2$ was required (Table 1, entry 13). Unfortunately, the reaction with *p*-chlorobenzyl alcohol (**2h**) resulted not in the expected arylation but in the formation of benzaldehyde by the palladium-catalyzed oxidation reaction (Table 1, entry 14).[10]

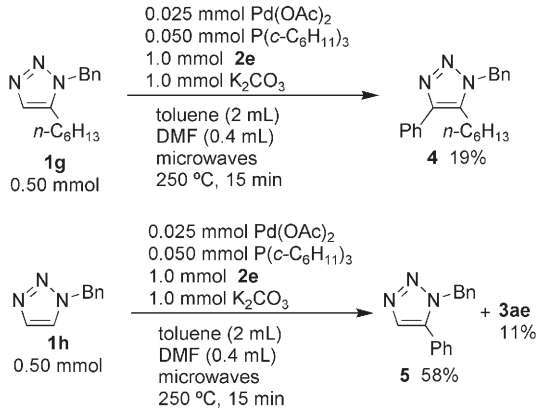
Triazole **1c**, which has a pyridyl group, underwent phenylation to afford the corresponding trisubstituted triazole in high yield (Table 1, entry 15). The reaction of **1d**, which bears a tertiary alcohol moiety, proceeded smoothly (Table 1, entry 16), whereas the presence of a hydroxymethyl group completely retarded the reaction (Table 1, entry 14). The reaction of 1-aryl-substituted **1e** afforded **3ee** quantitatively (Table 1, entry 17). The present approach to trisubstituted triazoles allowed for the selective preparation of two regioisomers, **3ai** and **3fe** (Scheme 1).



Scheme 1. Synthesis of 1,4,5-trisubstituted 1,2,3-triazole isomers **3ai** and **3fe**.

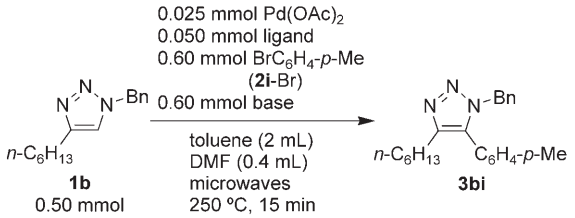
The reaction of 1-benzyl-5-hexyl-1,2,3-triazole (**1g**) was sluggish and provided **4** in only 19% yield (Scheme 2). Monosubstituted 1-benzyl-1,2,3-triazole (**1h**) reacted with chlorobenzene (**2e**) to give 5-phenyl-substituted product **5** predominantly, along with diphenyl-substituted **3ae** (Scheme 2). No 4-phenyl-substituted isomer was detected. The low reactivity of **1g** and the regioselectivity in the reaction of **1h** can be explained by the plausible mechanism described below.

Among the ligands screened, $P(c\text{-}C_6H_{11})_3$ proved to be the best (Table 2, entries 1–6). The molar ratio of $Pd(OAc)_2/P(c\text{-}C_6H_{11})_3$ had a significant influence on the yield, and a ratio of 1:2 was best (Table 2, entries 6–8). The yield depended heavily on the base used. Potassium carbonate and cesium carbonate promoted the reaction, whereas sodium carbonate was much less effective (Table 2, entries 6, 9, and 10).



Scheme 2. Reactions of 1,5-disubstituted and 1-monosubstituted 1,2,3-triazoles.

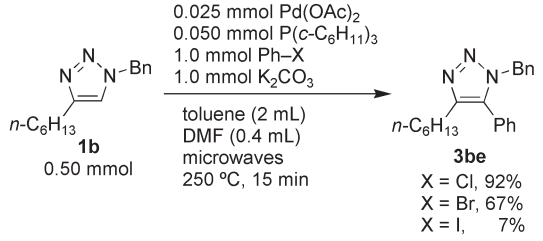
Table 2. Effect of ligand and base.



Entry	Ligand	Base	Yield [%]
1	PPh_3	Cs_2CO_3	56
2	PMe_3	Cs_2CO_3	54
3	$P(n\text{Bu})_3$	Cs_2CO_3	28
4	$P(t\text{Bu})_3$	Cs_2CO_3	52
5	$P(c\text{-}C_5H_9)_3$	Cs_2CO_3	7
6	$P(c\text{-}C_6H_{11})_3$	Cs_2CO_3	64
7	$P(c\text{-}C_6H_{11})_3$ (0.025 mmol)	Cs_2CO_3	12
8	$P(c\text{-}C_6H_{11})_3$ (0.075 mmol)	Cs_2CO_3	44
9	$P(c\text{-}C_6H_{11})_3$	K_2CO_3	77
10	$P(c\text{-}C_6H_{11})_3$	Na_2CO_3	14
11	$P(c\text{-}C_6H_{11})_3$	NaOAc	10
12	$P(c\text{-}C_6H_{11})_3$	Et_3N	7

Weaker bases such as sodium acetate and triethylamine failed to work (Table 2, entries 11 and 12). Palladium acetate was the best precursor, and other palladium salts such as $PdCl_2$, $Pd(OCOCF_3)_2$, $Pd(acac)_2$, $[Pd_2(dba)_3]$, and $[PdCl(\pi\text{-allyl})]_2$ (acac = acetyl acetonate, dba = dibenzylideneacetone) were much less active or completely inactive.

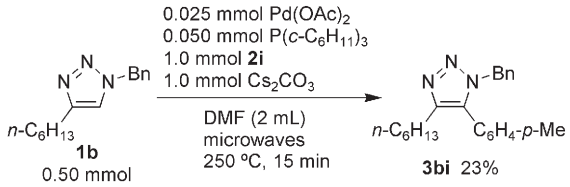
Notably, aryl chloride was superior to aryl bromide and iodide when $P(c\text{-}C_6H_{11})_3$ was used as a ligand (Scheme 3). A



Scheme 3. Scope of halogens in the aryl halides used.

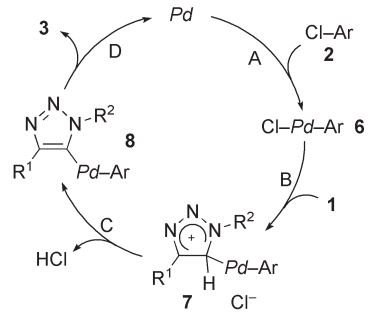
lower rate of oxidative addition of aryl chloride would be suitable for completing the catalytic cycle smoothly (see below).

The reaction in toluene alone was difficult to perform because microwaves could not heat the reaction mixture to 250 °C. The reaction in DMF alone afforded the product in very low yield, and most of the starting materials were recovered (Scheme 4).

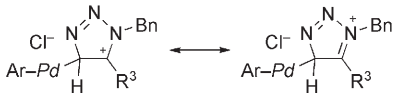


Scheme 4. Attempted reaction in DMF.

According to the literature,[5,8] a plausible mechanism is shown in Scheme 5. The key step is the reaction of the divalent arylpalladium species with triazole (step B), which generates a delocalized cationic intermediate **7**. The expanded delocalization would explain the facile arylation at the 5-position. The arylation at the 4-position would be unfavorable because of the more localized stabilization of the cationic charge formed (Scheme 6).



Scheme 5. Plausible catalytic cycle.



Scheme 6. Plausible cationic intermediate for arylation at the 4-position of triazoles.

It was reported that microwave heating is different from conventional external heating and can have so-called nonthermal microwave effects.[11] This is also the case for the present reaction (Scheme 7). The reaction of **1b** with **2e** was completed smoothly and quantitatively within 15 min in 1,2-diphenylethane (b.p.: 284 °C)/*N*,*N*′-dimethylpropylene urea (DMPU; b.p.: 146 °C/44 mmHg) by using microwave heating at 250 °C, whereas the same reaction hardly proceeded by classical heating for 30 min at 250 °C. A similar microwave

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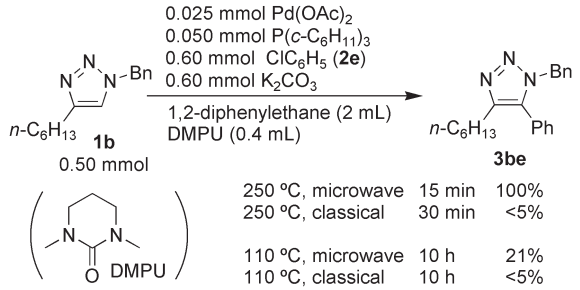

Scheme 7. The nonthermal microwave effect.

effect was observed when the reactions were performed at 110 °C for 10 h. It is difficult to explain how nonthermal microwave effects operate in the present system. Possible nonthermal microwave effects may be: 1) microwave-assisted activation of the polar transition state of step B, which is probably rate-determining, 2) prevention of the formation of palladium black, and 3) intervention of localized microscopic high temperatures.[11]

Conclusions

We have developed the microwave-assisted palladium-catalyzed direct arylation of 1,4-disubstituted 1,2,3-triazoles with aryl chloride. Copper-catalyzed formal [3+2] cycloaddition of terminal alkynes with organic azides efficiently provided a variety of 1,4-disubstituted 1,2,3-triazoles. The present reaction thus offers a concise and rapid synthesis of 1,4,5-trisubstituted 1,2,3-triazoles.

Experimental Section

General

Unless otherwise noted, all reactions were carried out with a focused microwave unit (Biotage Initiator™). The maximum irradiation power was 400 W. Each reaction was run in a 5-mL glass pressure vial, which is a commercially available vial specially made for the Biotage Initiator™. It took 6 min to reach 250 °C. After the indicated temperatures were reached, controlled microwave irradiation started and was continued for 15 min to keep the reaction temperature constant. The classical heating at 250 and 110 °C shown in Scheme 7 was performed in glassware heated in a sand bath and an oil bath, respectively.

^{1}H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were recorded in $CDCl_3$ on a Varian UNITY INOVA 500 spectrometer. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane at 0.00 ppm for ^{1}H and $CDCl_3$ at 77.0 ppm for ^{13}C, unless otherwise noted. IR spectra were recorded on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were recorded on a JEOL Mstation 700 spectrometer. TLC analysis was performed on commercial glass plates with a 0.25-mm layer of Merck silica gel 60F_{254}. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analysis was carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene was stored over slices of sodium. Palladium acetate and tricyclohexylphosphine were obtained from TCI. Tricyclohexylphosphine was diluted to 0.50 M in toluene and stored under argon. Triazoles **1a–f** were prepared under copper catalysis according to the literature.[1] Triazole **1g** was prepared by the reported procedure.[4] Triazole **1h** was prepared in 58% yield by treatment of 1,2,3-triazole with benzyl bromide (2 equiv) in the presence of potassium carbonate (2 equiv) in refluxing acetone for 24 h.

Caution: Organic azides can be explosive. Only a small amount of material should be prepared. We prepared the azide compounds on the 5-mmol scale. They should be handled with care.

Syntheses

Typical procedure for the arylation reaction: The reaction in Table 1, entry 2 is representative. Potassium carbonate (83 mg, 0.60 mmol), palladium acetate (5.6 mg, 0.025 mmol), and **1a** (120 mg, 0.50 mmol) were placed in a 5-mL glass pressure vial. The vial was flushed with argon and sealed with a polytetrafluoroethylene (PTFE)/silicone septum. Toluene (2.0 mL) and tricyclohexylphosphine (0.50 M in toluene, 0.10 mL, 0.050 mmol) were added, and the mixture was stirred for 1 min. Ethyl *p*-chlorobenzoate (**2b**; 94 μL, 0.60 mmol) and DMF (0.40 mL) were added. The suspension was heated at 250 °C with stirring for 15 min in the microwave reactor. The mixture was then cooled to room temperature. Hydrochloric acid (1 M, 3 mL) was added, and the product was extracted with ethyl acetate (3×5 mL). The organic layer was then washed with brine (5 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated. Purification by silica-gel column chromatography (hexane/ethyl acetate = 3:1) provided **3ab** (0.16 g, 0.42 mmol) in 84% yield.

Compounds **1a**,[2] **1e**,[12] **1h**,[13] **3ac**,[14] **3ae**,[2] and **3ee**[15] showed spectra identical to those reported in the literature.

1b: 1-Benzyl-4-hexyl-1,2,3-triazole: M.p.: 54.9–55.6 °C; IR (nujol): $\tilde{\nu}$ = 1557, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, J = 7.0 Hz, 3H), 1.26–1.36 (m, 6H), 1.63 (quint, J = 7.5 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 5.49 (s, 2H), 7.17 (s, 1H), 7.23–7.27 (m, 2H), 7.32–7.38 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 22.7, 25.9, 29.1, 29.5, 31.7, 54.1, 120.6, 128.1, 128.8, 129.2, 135.2, 149.2 ppm; elemental analysis: calcd (%) for $C_{15}H_{21}N_3$: C 74.04, H 8.70; found: C 74.16, H 8.76.

1c: 1-Benzyl-4-(4-pyridyl)-1,2,3-triazole: M.p.: 127.9–129.1 °C; IR (nujol): $\tilde{\nu}$ = 1610, 1563, 1208, 1087, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 5.60 (s, 2H), 7.32–7.34 (m, 2H), 7.39–7.43 (m, 3H), 7.68 (d, J = 6.0 Hz, 2H), 7.79 (s, 1H), 8.64 ppm (d, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 54.6, 120.1, 121.1, 128.4, 129.2, 129.5, 134.4, 138.0, 145.9, 150.6 ppm; elemental analysis: calcd (%) for $C_{14}H_{12}N_4$: C 71.17, H 5.12; found: C 71.32, H 5.08.

1d: 1-Benzyl-4-(2-butyl-2-hydroxyhexyl)-1,2,3-triazole: M.p.: 69.9–70.1 °C; IR (nujol) $\tilde{\nu}$ = 3372, 3123 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, J = 7.0 Hz, 6H), 1.28–1.65 (m, 12H), 2.17 (s, 2H), 2.75 (br s, 1H), 5.51 (s, 2H), 7.22–7.23 (m, 2H), 7.32–7.39 ppm (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 23.2, 25.9, 35.3, 39.0, 54.4, 74.1, 124.3 (br), 127.9, 128.6, 129.0, 134.9, 146.9 ppm (br); elemental analysis: calcd (%) for $C_{19}H_{29}N_3O$: C 72.34, H 9.27; found: C 72.19, H 9.09.

1f: 1-Benzyl-4-(*p*-tolyl)-1,2,3-triazole: M.p.: 151.4–152.6 °C; IR (nujol): $\tilde{\nu}$ = 1221, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 2.36 (s, 3H), 5.57 (s, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.30–7.32 (m, 2H), 7.37–7.41 (m, 3H), 7.62 (s, 1H), 7.69 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.4, 54.4, 119.3, 125.8, 127.9, 128.2, 128.9, 129.3, 129.6, 134.9, 138.2, 148.5 ppm; elemental analysis: calcd (%) for $C_{16}H_{15}N_3$: C 77.08, H 6.06; found: C 76.78, H 5.99.

1g: 1-Benzyl-5-hexyl-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2931, 1457, 1237 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 0.78 (t, J = 7.0 Hz, 3H), 1.10–1.22 (m, 6H), 1.44 (quint, J = 7.5 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 5.43 (s, 2H), 7.07–7.08 (m, 2H), 7.21–7.28 (m, 3H), 7.41 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.5, 23.2, 27.9, 28.8, 31.4, 51.7, 127.2, 128.3, 129.0, 132.7, 135.2, 137.6 ppm; elemental analysis: calcd (%) for $C_{15}H_{21}N_3$: C 74.04, H 8.70; found: C 73.80, H 8.92%.

3aa: 1-Benzyl-4-phenyl-5-(*o*-tolyl)-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 1457, 1353, 1244, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 1.61 (s, 3H), 5.27 (d, J = 15.0 Hz, 1H), 5.36 (d, J = 15.0 Hz, 1H), 6.94–6.96 (m, 2H), 7.09–7.11 (m, 1H), 7.18–7.13 (m, 8H), 7.40–7.43 (m, 1H), 7.53–7.55 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 19.2, 52.4, 125.9, 126.7, 127.6, 127.8, 128.2, 128.4, 128.7, 128.7, 130.3, 130.5, 130.9, 131.4, 133.0, 134.9, 138.6, 144.6 ppm; elemental analysis: calcd (%) for $C_{22}H_{19}N_3$: C 81.20, H 5.86; found: C 81.47, H 5.91%.

3ab: 1-Benzyl-5-(*p*-ethoxycarbonylphenyl)-4-phenyl-1,2,3-triazole: M.p.: 108.8–110.1; IR (nujol): $\tilde{\nu}$ = 1715, 1273 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.42 (t, J = 7.0 Hz, 3H), 4.42 (q, J = 7.0 Hz, 2H), 5.43 (s, 2H), 7.01–7.03 (m, 2H), 7.22–7.26 (m, 8H), 7.51 (d, J = 8.0 Hz, 2H), 8.08 ppm (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.4, 52.4, 61.6, 126.9, 127.5, 128.1, 128.4, 128.7, 128.9, 130.3, 130.4, 130.6, 131.9, 132.6, 133.0, 135.2, 145.1, 166.0 ppm; elemental analysis: calcd (%) for $C_{24}H_{21}N_3O_2$: C 75.18, H 5.52; found: C 73.35, H 5.54%.

3ad: 5-{*p*-(Acetoxymethyl)phenyl}-1-benzyl-4-phenyl-1,2,3-triazole: M.p.: 107.1–108.4 °C; IR (nujol): $\tilde{\nu}$ = 1741, 1252 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.17 (s, 3H), 5.18 (s, 2H), 5.41 (s, 2H), 7.03–7.05 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.24–7.29 (m, 6H), 7.39 (d, J = 8.0 Hz 2H), 7.54–7.56 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.2, 52.2, 65.7, 127.0, 127.6, 127.8, 128.0, 128.4, 128.7, 128.7, 128.9, 130.5, 131.0, 133.6, 135.5, 137.9, 144.8, 170.9 ppm; elemental analysis: calcd (%) for $C_{24}H_{21}N_3O_2$: C 75.18, H 5.52; found: C, 74.88 H, 5.46.

3af: 1-Benzyl-5-(*o*-biphenylyl)-4-phenyl-1,2,3-triazole: M.p.: 124.9–126.1 °C; IR (nujol): $\tilde{\nu}$ = 1607, 1496, 1354, 1242 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.88 (d, J = 15.0 Hz, 1H), 5.27 (d, J = 15.0 Hz, 1H), 6.89–6.91 (m, 4H), 7.11–7.28 (m, 10H), 7.35 (td, J = 7.0, 2.0 Hz, 1H), 7.54–7.60 ppm (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 52.2, 126.2, 126.5, 127.5, 127.7, 128.0, 128.0, 128.2, 128.4, 128.5, 128.5, 128.6, 130.4, 130.9, 131.1, 131.7, 133.2, 134.8, 139.5, 142.4, 145.3 ppm; elemental analysis: calcd (%) for $C_{27}H_{21}N_3$: C 83.69, H 5.46; found: C 83.82, H 5.39.

3ag: 1-Benzyl-5-(2,6-dimethylphenyl)-4-phenyl-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 1608, 1498, 1352, 1243 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.67 (s, 6H), 5.21 (s, 2H), 6.97 (d, J = 7.0 Hz, 2H), 7.12 (d, J = 7.0 Hz, 2H), 7.17–7.25 (m, 6H), 7.34 (t, J = 7.5 Hz, 1H), 7.55 ppm (dt, J = 6.5, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 19.6, 52.5, 125.3, 127.0, 127.7, 128.2, 128.5, 128.6, 128.7, 128.7, 130.2, 131.3, 132.0, 134.4, 138.5, 144.0 ppm; elemental analysis: calcd (%) for $C_{23}H_{21}N_3$: C 81.38, H 6.24; found: C 81.22, H 6.29.

3ba: 1-Benzyl-4-hexyl-5-(*o*-tolyl)-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2928, 1456 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.81 (t, J = 7.0 Hz, 3H), 1.14–1.31 (m, 6H), 1.56 (quint, J = 7.5 Hz, 2H), 1.72 (s, 3H), 2.40 (quint, J = 7.5 Hz, 1H), 2.54 (quint, J = 7.5 Hz, 1H), 5.22 (d, J = 14.5 Hz, 1H), 5.27 (d, J = 14.5 Hz, 1H), 6.89–6.96 (m, 3H), 7.15–7.23 (m, 5H), 7.34–7.37 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 19.3, 22.7, 25.4, 29.1, 29.2, 31.6, 52.4, 126.2, 127.1, 128.2, 128.2, 128.6, 129.9 130.5, 130.8, 133.6, 135.2, 138.5, 146.6 ppm; elemental analysis: calcd (%) for $C_{22}H_{27}N_3$: C 79.24, H 8.16; found: C 79.37, H 8.25.

3bb: 1-Benzyl-5-(*p*-ethoxycarbonylphenyl)-4-hexyl-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2930, 1718, 1275, 1107 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.82 (t, J = 7.0 Hz, 3H), 1.18–1.26 (m, 6H), 1.41 (t, J = 7.0 Hz, 3H), 1.61 (quint, J = 7.5 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 5.41 (s, 2H), 6.98–7.00 (m, 2H), 7.19 (d, J = 7.5 Hz, 2H), 7.23–7.25 (m, 3H), 8.07 ppm (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 14.5, 22.7, 25.3, 29.1, 29.7, 31.6, 52.3, 61.5, 127.4, 128.3, 128.9, 129.8, 130.1, 131.3, 132.4, 133.6, 135.6, 146.7, 166.1 ppm; elemental analysis: calcd (%) for $C_{24}H_{29}N_3O_2$: C 73.63, H 7.47; found: C 73.58, H 7.44.

3bc: 1-Benzyl-4-hexyl-5-(*p*-methoxyphenyl)-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2930, 1507, 1252 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.82 (t, J = 7.0 Hz, 3H) 1.16–1.29 (m, 6H), 1.62 (quint, J = 7.5 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H), 3.84 (s, 3H), 5.37 (s, 2H), 6.91–6.93 (m, 2H), 7.00–7.03 (m, 4H), 7.23–7.26 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 22.7, 25.3, 29.1, 29.7, 31.6, 52.0, 55.5, 114.4, 119.7, 127.5, 128.1, 128.8, 131.2, 134.3, 136.0, 146.2, 160.4 ppm; elemental analysis: calcd (%) for $C_{22}H_{27}N_3O$: C 75.61, H 7.79; found: C 75.84, H 7.81.

3bd: 5-{*p*-(Acetoxymethyl)phenyl}-1-benzyl-4-hexyl-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2930, 1744, 1227, 1030 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.82 (t, J = 7.0 Hz, 3H), 1.16–1.31 (m, 6H), 1.62 (quint, J = 7.5 Hz, 2H), 2.14 (s, 3H), 2.59 (t, J = 7.5 Hz, 2H), 5.15 (s, 2H), 5.39 (s, 2H), 6.99–7.01 (m, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.24–7.25 (m, 3H), 7.39 ppm (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 21.1, 22.7, 25.2, 29.1, 29.7, 31.6, 52.1, 65.7, 127.4, 127.6, 128.2, 128.5, 128.8, 130.0, 134.1, 135.8, 137.3, 146.4, 170.9 ppm; elemental analysis: calcd (%) for $C_{24}H_{29}N_3O_2$: C 73.63, H 7.47; found: C 73.35, H 7.52.

3be: 1-Benzyl-4-hexyl-5-phenyl-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2929, 1455 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.82 (t, J = 7.0 Hz, 3H), 1.16–1.28 (m, 6H), 1.62 (quint, J = 8.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 5.40 (s, 2H), 6.98–7.01 (m, 2H), 7.10–7.12 (m, 2H), 7.22–7.25 (m, 3H), 7.38–7.44 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 22.7, 25.2, 29.1, 29.7, 31.6, 52.1, 127.5, 127.8, 128.1, 128.8, 129.0, 129.3, 129.8, 134.5, 135.9, 146.3 ppm; elemental analysis: calcd (%)for $C_{21}H_{25}N_3$: C 78.96, H 7.89; found: C 79.02, H 7.93.

3ce: 1-Benzyl-5-phenyl-4-(4-pyridyl)-1,2,3-triazole: M.p.: 155.4–156.7 °C; IR (nujol): $\tilde{\nu}$ = 1602 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.41 (s, 2H), 7.01–7.03 (m, 2H), 7.14–7.16 (m, 2H), 7.24–7.28 (m, 3H), 7.41–7.47 (m, 4H), 7.53–7.56 (m, 1H), 8.48 ppm (d, J = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 52.4, 120.7, 127.2, 127.8, 128.5, 129.0, 129.7, 130.0, 130.5, 135.1, 138.8, 138.8, 142.1, 150.1 ppm; elemental analysis: calcd (%) for $C_{20}H_{16}N_4$: C 76.90, H 5.16; found: C 76.79, H 5.20.

3de: 1-Benzyl-4-(2-butyl-2-hydroxyhexyl)-5-phenyl-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 3448, 2955, 1456, 1240 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.80 (t, J = 7.5 Hz, 6H), 1.04–1.43 (m, 12H), 2.73 (s, 2H), 3.82 (s, 1H), 5.43 (s, 2H), 6.97–7.00 (m, 2H), 7.09–7.11 (m, 2H), 7.22–7.26 (m, 3H), 7.40–7.47 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 23.4, 26.1, 34.2, 38.9, 52.3, 74.5, 127.3, 127.5, 128.3, 128.9, 129.2, 129.7, 129.9, 135.6, 136.0, 143.4 ppm; HRMS (FAB): m/z calcd for $C_{25}H_{33}N_3O$: 391.2624; found: 391.2617.

3fe: 1-Benzyl-5-phenyl-4-(*p*-tolyl)-1,2,3-triazole: M.p.: 125.8–127.0 °C; IR (nujol): $\tilde{\nu}$ = 1256, 1156, 1064 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 5.41 (s, 2H), 7.02–7.04 (m, 2H), 7.06–7.08 (m, 2H), 7.13–7.16 (m, 2H), 7.24–7.27 (m, 3H), 7.39–7.49 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 21.4, 52.2, 126.8, 127.6, 128.1, 128.2, 128.3, 128.8, 129.3, 129.3, 129.7, 130.3, 133.7, 135.6, 137.6, 144.8 ppm; elemental analysis: calcd (%) for $C_{22}H_{19}N_3$: C 81.20, H 5.86; found: C 80.97, H 5.90.

3ai: 1-Benzyl-4-phenyl-5-(*p*-tolyl)-1,2,3-triazole: M.p.: 113.2–114.9 °C; IR (nujol): $\tilde{\nu}$ = 1366, 1313, 1016 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.43 (s, 3H), 5.40 (s, 2H), 7.04–7.08 (m, 4H), 7.21–7.28 (m, 8H), 7.60–7.62 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 21.5, 51.9, 124.7, 126.7, 127.5, 127.6, 128.1, 128.4, 128.7, 129.9, 130.0, 131.1, 134.1, 135.6, 139.8, 144.4 ppm; elemental analysis: calcd (%) for $C_{22}H_{19}N_3$: C 81.20, H 5.86; found: C 80.93, H 5.94.

3bi: 1-Benzyl-4-hexyl-5-(*p*-tolyl)-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2927, 1455 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.82 (t, J = 7.0 Hz, 3H), 1.17–1.29 (m, 6H), 1.62 (quint, J = 7.5 Hz, 2H), 2.40 (s, 3H), 2.60 (t, J = 7.5 Hz, 2H), 5.38 (s, 2H), 6.99–7.02 (m, 4H), 7.20–7.26 ppm (m, 5H); ^{13}C NMR ($CDCl_3$): δ = 14.0, 21.3, 22.5, 25.1, 28.9, 29.6, 31.5, 51.8, 124.6, 127.3, 127.9, 128.6, 129.5, 129.6, 134.4, 135.8, 139.2, 146.0 ppm.; elemental analysis: calcd (%) for $C_{22}H_{27}N_3$: C 79.24, H 8.16; found: C 78.99, H 8.14.

4: 1-Benzyl-5-hexyl-4-phenyl-1,2,3-triazole: IR (neat): $\tilde{\nu}$ = 2930, 1497, 1245 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.83 (t, J = 7.0 Hz, 3H), 1.12–1.26 (m, 6H), 1.35 (quint, J = 8.0 Hz, 2H), 2.71 (t, J = 8.0 Hz, 2H), 5.56 (s, 2H), 7.21 (d, J = 7.0 Hz, 2H), 7.32–7.37 (m, 4H), 7.43 (t, J = 8.0 Hz, 2H), 7.71 ppm (d, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.6, 23.4, 28.5, 29.2, 31.3, 52.2, 127.2, 127.3, 127.8, 128.5, 128.8, 129.1, 132.0, 133.9, 135.5, 144.9 ppm; elemental analysis: calcd (%) for $C_{21}H_{25}N_3$: C 78.96, H 7.89; found: C 79.02, H 7.93.

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[1] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708–2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; b) C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.

[2] L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.

CHEMISTRY
AN ASIAN JOURNAL

[3] a) S. Díez-González, A. Correa, L. Cavallo, S. P. Nolan, *Chem. Eur. J.* **2006**, *12*, 7558–7564; b) M. Majireck, S. M. Weinreb, *J. Org. Chem.* **2006**, *71*, 8680–8683, and references cited therein.
[4] A. Krasinski, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237–1240.
[5] a) *Handbook of C–H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, Germany, **2005**; b) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; c) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; d) M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211–241; e) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200–205; f) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; g) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193.
[6] Reviews for microwave-assisted organic reactions: a) *Microwave Assisted Organic Synthesis* (Eds.: J. P. Tierney, P. Lidström), Blackwell Publishing, Victoria, **2005**; b) *Microwave Methods in Organic Synthesis* (Eds.: M. Larhed, K. Olofsson), Springer-Verlag, Berlin, **2006**; c) B. A. Roberts, C. R. Strauss, *Acc. Chem. Res.* **2005**, *38*, 653–661; d) H. Tokuyama, M. Nakamura, *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 523–538; e) A. de La Hoz, A. Diaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164–178; f) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408–6443; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284; g) P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, *57*, 9225–9283; h) S. Caddick, *Tetrahedron* **1995**, *51*, 10403–10432; i) D. M. P. Mingos, D. R. Baghurst, *Chem. Soc. Rev.* **1991**, *20*, 1–47.
[7] Examples of the use of aryl chlorides in direct arylation of heterocycles: a) Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara, M. Shimizu, *Heterocycles* **1985**, *23*, 2327–2333; b) R. D. Rieth, N. P. Mankad, E. Calimano, J. P. Sadighi, *Org. Lett.* **2004**, *6*, 3981–3983.
[8] S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333–2336.
[9] H. A. Chiong, O. Daugulis, *Org. Lett.* **2007**, *9*, 1449–1451.
[10] a) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, *64*, 6750–6755; b) K. P. Peterson, R. C. Larock, *J. Org. Chem.* **1998**, *63*, 3185–3189; c) J. Muzart, *Tetrahedron* **2003**, *59*, 5789–5816.
[11] a) S. Garbacia, B. Desai, O. Lavastre, C. O. Kappe, *J. Org. Chem.* **2003**, *68*, 9136–9139; b) L. Perreux, A. Loupy, *Tetrahedron* **2001**, *57*, 9199–9223; c) N. Kuhnert, *Angew. Chem.* **2002**, *114*, 1943–1946; *Angew. Chem. Int. Ed.* **2002**, *41*, 1863–1866; d) C. R. Strauss, *Angew. Chem.* **2002**, *114*, 3741–3743; *Angew. Chem. Int. Ed.* **2002**, *41*, 3589–3590.
[12] Y.-B. Zhao, Z.-Y. Yan, Y.-M. Liang, *Tetrahedron Lett.* **2006**, *47*, 1545–1549.
[13] W. Holzer, *Tetrahedron* **1991**, *47*, 9783–9792.
[14] J. Deng, Y.-M. Wu, Q.-Y. Chen, *Synthesis* **2005**, 2730–2738.
[15] Z.-X. Wang, H.-L. Qin, *Chem. Commun.* **2003**, 2450–2451.

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