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Palladium-Catalyzed C–H Arylation of Amides by Triazole Assistance

Darko Santrač,‘ Stefano Cella,‘ Wei Wang, and Lutz Ackermann*[a]

Abstract: Versatile palladium-catalyzed C–H arylations of benzamides were accomplished by triazole amine (TAM) assistance. The robustness of the palladium-catalyzed C–H functionalization protocol was reflected by its broad functional group tolerance, ample substrate scope and C–H arylations under silver-free reaction conditions.

Introduction

Transition metal-catalyzed arylations of unactivated C–H bonds[1] have emerged as transformative alternatives to traditional cross-coupling reactions of prefunctionalized substrates.[2] The control of positional selectivity represents the key challenge in the development of synthetically meaningful intermolecular C–H transformations, with considerable progress realized by chelation-assisted C–H activation.[3] Indeed, particularly bidentate directing groups have proven instrumental for site-selective C–H functionalizations by palladium catalysis,[4] with major contributions by inter alia Daugulis, Chatani and Shi using 8-aminoquinoline (AQ) and (pyridin-2-yl)isopropyl (PIP) amine-derived auxiliaries.[5]

The copper-catalyzed[6] 1,3-dipolar cycloaddition[7] has been identified as a powerful tool for the late-stage diversification in medicinal chemistry, material sciences and biomolecular chemistry.[8] With the prospect of providing an additional element of complexity-increasing structural diversification, in 2008,[9] we have introduced 1,2,3-trazoles as directing groups in positional-selective C–H functionalizations.[10] Guided by these findings, we had developed modular triazole amines (TAM), which inter alia enabled iron-[11] and ruthenium-catalyzed[12] arylations, alkenylations and alkylations.[13] Within our own program on palladium-catalyzed C–H arylations,[14] we have now explored the use of TAM amides for site-selective palladium-catalyzed C–H arylations, on which we report herein. Notable features of our strategy are not limited to (i) efficient palladium-catalyzed C–H arylations, under (ii) silver-free reaction conditions, and (iii) a facile removal[15] of the TAM group in a traceless fashion.

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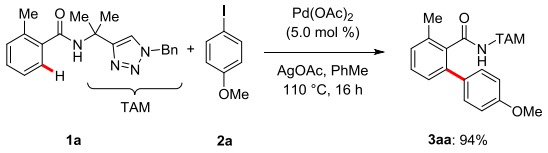
Results and Discussion

Optimization

At the outset, we explored reaction conditions for the desired C–H arylation of TAM-amide **1a** (Table 1, and S-1 in the Supporting Information).[16] Hence, the desired C–H functionalization occurred at reaction temperatures as low as 60 °C, with optimal results being achieved at elevated temperatures (entries 1–4). High catalytic efficacy was guaranteed by the use of AgOAc as the additive, but silver(I)-free reaction conditions proved also viable (*vide infra*, entries 5–7).

Table 1. Optimization of the palladium-catalyzed C–H arylation of amide **1a**[a]

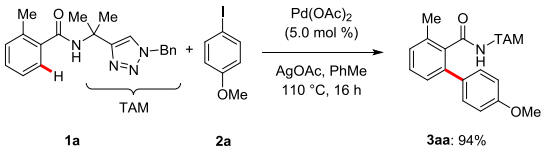


1a **2a** **3aa**: 94%

Entry	Variation from standard condition	Yield [%][a]
1	---	94
2	60 °C	35
3	80 °C	80
4	150 °C	95
5	NaOAc instead of AgOAc	---
6	Me_4NCl, nBu_4NF, or nBu_4NI instead of AgOAc	---
7	KOAc/Me_4NCl instead of AgOAc	50[b]

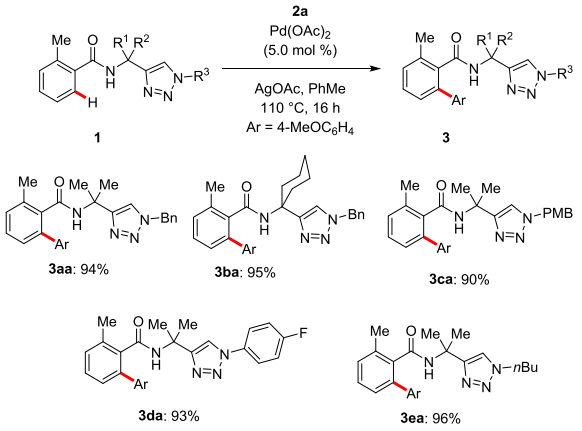
[a] Reaction conditions: **1a** (0.50 mmol), **2a** (2.00 mmol), $Pd(OAc)_2$ (5.0 mol %), AgOAc (1.10 equiv), PhMe (4.0 mL), 16h, 110 °C. [b] **1a** (0.50 mmol), **2a** (2.00 mmol), $Pd(OAc)_2$ (5.0 mol %), KOAc (2.8 equiv), Me_4NCl (2.05 equiv), AcOH (1.5 equiv), 48 h, 120 °C.

Thus, the optimization studies identified $Pd(OAc)_2$ as the optimal catalyst, along with AgOAc as the additive of choice (Scheme 1).



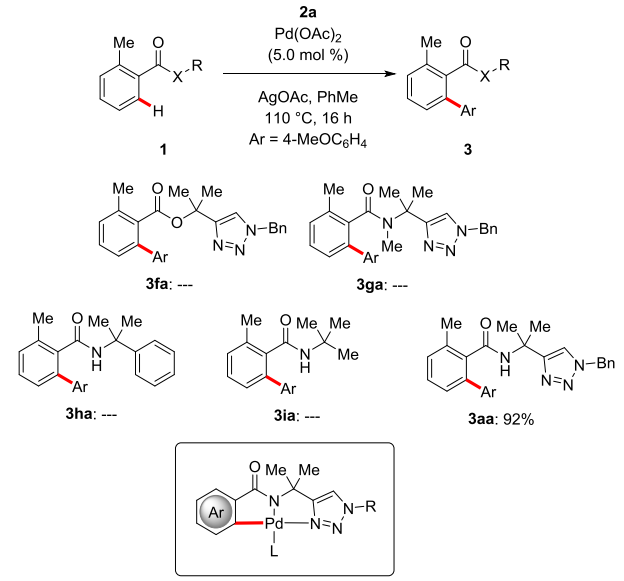
Scheme 1. Optimized palladium-catalyzed C–H arylation by TAM assistance.

With the optimized reaction conditions in hand, we tested its versatility in the palladium-catalyzed C–H arylation of amides **1** that possess differently decorated TAM motifs (Scheme 2). Interestingly, a considerable structural diversification on the 1,2,3-triazole scaffold was well accepted, thereby providing the desired products **3aa**–**3ea** in excellent yields.



Scheme 2. Influence of the TAM substitution pattern on C–H arylation.

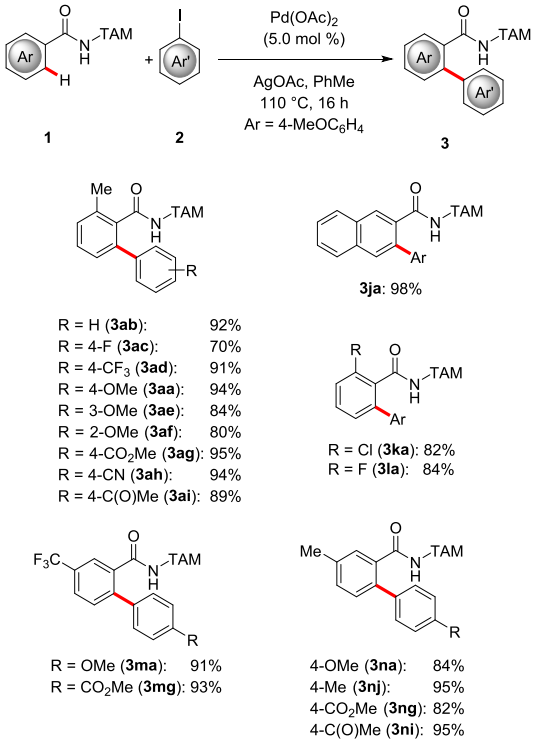
The coordination mode of the TAM group was thereafter probed by attempted palladium-catalyzed C–H arylations with the corresponding ester **1f** and the tertiary amide **1g**, highlighting the importance of the *NH*-acidic secondary amide functionality. Likewise, the secondary amides **1h** and **1i** being devoid of the Lewis-basic 1,2,3-triazole motif failed to furnish the C–H arylated products (Scheme 3), revealing the bidentate coordination of the TAM-amides **1a**. Overall, these findings provide strong support for a mono-anionic *N*,*N*-bidentate binding of the TAM amide to the palladium(II) center.



Scheme 3. Support for a mono-anionic bidentate coordination mode.

Substrate Scope

Encouraged by these results, we next explored the catalyst's versatility in the C–H arylation process (Scheme 4). Indeed, the C–H functionalization protocol proved applicable to differently substituted aryl iodides **2a-i**, including sterically demanding *ortho*-substituted derivatives. A variety of valuable electrophilic functional groups, such as chloro, ester or ketone substituents, was fully tolerated on the aryl iodides **2**, thereby providing a handle for further post-synthetic manipulation. The palladium-catalyzed C–H arylation occurred with high positional selectivity within intramolecular competition experiments, solely cleaving the less sterically congested C–H bonds to furnish products **3ma**, **3mg** and **3na**–**3ni**.

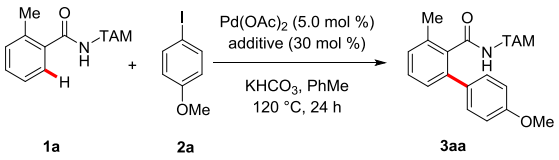


Scheme 4. Scope of TAM-assisted C–H arylation.

Silver-Free C–H Functionalization

Given that the use of expensive silver(I) salts[17] as additives generates undesired metal by-products, we became attracted to establishing silver-free reaction conditions for the TAM-assisted C–H arylation. To this end, we probed various additives in the palladium-catalyzed C–H functionalization of amide **1a**, employing the mild base $KHCO_3$ (Table 2). While catalytic amounts of acetates allowed for the synthesis of desired biaryl amide **3aa** (entries 1–3), optimal results were accomplished with adamantyl and pivaloyl carboxylic acids (entries 4–6). These observations can be rationalized in terms of carboxylate-assisted[18] C–H activation being operative via a concerted metalation−deprotonation (CMD),[19] ambiphilic metal-ligand activation (AMLA),[20] or base-assisted intra-molecular electrophilic substitution-type (BIES)[21] transition state.

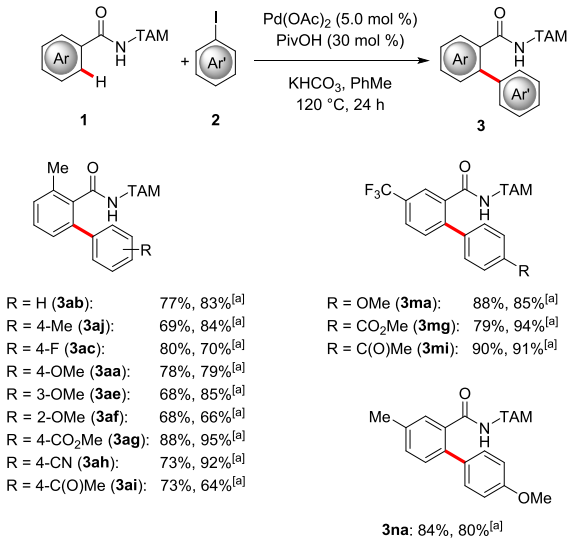
Table 2. Optimization of the silver-free C–H arylation[a]



entry	additive	**3aa** [%][b]
1	---	
2	NaOAc	53
3	CsOAc	77
4	$MesCO_2H$	80
5	$(1\text{-Ad})CO_2H$	89
6	PivOH	83

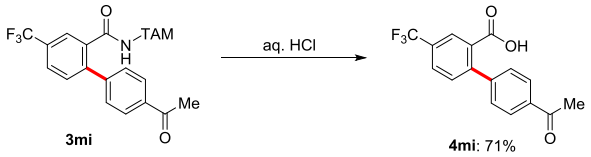
[a] Reaction conditions: **1a** (0.50 mmol), **2a** (1.00 mmol), $Pd(OAc)_2$ (5.0 mol %), additive (30 mol %), PhMe (4.0 mL), 24h, 120 °C. [b] NMR conversion with CH_2Br_2 as internal standard.

Subsequently, the scope of the silver-free palladium-catalyzed C–H arylation of TAM-amides **1** was explored. Indeed, the optimized protocol turned out to be widely applicable (Scheme 5). Thus, *para*-, *meta*- and even sterically encumbered *ortho*-substituted aryl iodides **2** were fully tolerated. Moreover, valuable electrophilic functionalities, including ester, cyano and ketone groups, were accepted by the optimized catalytic system. In contrast, aryl bromides and chlorides were as of yet not suitable substrates. The palladium-catalyzed C–H functionalization was characterized by high *ortho*-selectivity, as became evident within TAM-assisted C–H arylations on the *meta*-substituted substrates **1m** and **1n**.



Scheme 5. Silver-free C–H arylations of TAM-amides **1**. [a] 1-AdCO$_2$H as the additive.

The practical utility of our strategy was illustrated by the removal of the TAM group[11] in a traceless[15] fashion to deliver the biaryl carboxylic acid **4** in high yield, featuring the sensitive ketone functionality (Scheme 6).



Scheme 6. TAM removal in a traceless fashion.

Conclusions

In summary, we have reported on the unprecedented palladium-catalyzed C–H arylation by TAM-assistance. Thus, an operationally simple C–H functionalization of TAM-amides was accomplished with excellent functional group tolerance and ample substrate scope. The removable TAM-group enabled silver-free C–H arylations with KHCO$_3$ as a mild[22] base through a carboxylate assistance manifold.

Experimental Section

General Remarks

Catalytic reactions were carried out in Schlenk tubes under a N_2 atmosphere using pre-dried glassware. Toluene was dried over Na and distilled under N_2. All starting materials were synthesized according to previously described methods.[12a] *N*-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-2-fluorobenzamide, was prepared according to a literature procedure.[12a] Other chemicals were obtained from commercial sources and were used without further purification, except aryl iodides, which were sublimed twice before their use. Yields refer to isolated compounds, estimated to be > 95% pure as determined by ^{1}H-NMR and GC-analysis. Chromatography: Merck silica gel 60 (40-63 µm). NMR: Spectra were recorded on Varian Unity 300, Mercury 300, Inova 500, or Inova 600 in the solvent indicated; chemical shifts (δ) are given in ppm. All IR spectra were recorded on a Bruker FT-IR Alpha device. MS: EI-MS-spectra were recorded with Finnigan MAT 95, 70 eV; High resolution mass spectrometry (HRMS) with APEX IV 7T FTICR, Bruker Daltonic. M. p.: Stuart melting point apparatus SMP3, Barlworld Scientific, values are uncorrected.

Representative Procedure A for Palladium-Catalyzed C–H Arylation

A mixture of amide **1** (0.50 mmol), aryl iodide **2** (2.00 mmol), Pd(OAc)$_2$ (5.0 mol %), AgOAc (0.55 mmol) and PhMe (4.0 mL) under N_2 was stirred at 110 °C for 16 h. At ambient temperature, the mixture was diluted with EtOAc (20 mL), stirred for 10 minutes, filtered through a plug of celite (0.5 × 3.0 cm), and the plug was washed with EtOAc (100 mL). The resulting solution was concentrated *in vacuo*, and purified by column chromatography on silica gel.

Representative Procedure B for Silver-free Palladium-Catalyzed C–H Arylation

A mixture of amide **1** (0.50 mmol), aryl iodide **2** (1.00 mmol), Pd(OAc)$_2$ (5.0 mol %), KHCO$_3$ (2.00 equiv), PivOH (30 mol %) in PhMe (4.0 mL) under N_2 was stirred at 120 °C for 24 h. At ambient temperature, the mixture was diluted with EtOAc (20 mL), stirred for 10 minutes, filtered through a plug of celite (0.5 × 3.0 cm), and the plug was washed with EtOAc (100 mL). The resulting solution was concentrated in vacuo, and purified by column chromatography on silica gel.

N-(2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl)-4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxamide (3aa)

The representative procedure A was followed using **1a** (167 mg, 0.5 mmol), 4-iodoanisole (**2a**) (468 mg, 2.00 mmol), Pd(OAc)$_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), and AgOAc (91.8 mg, 0.55 mmol). Column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3aa** (207 mg, 94%) as a pale yellow solid. M.p.: 114–115 °C. ^{1}H-NMR (600 MHz, CDCl$_3$) δ (ppm) = 7.35–7.29 (m, 5H), 7.25–7.19 (m, 4H), 7.10 (t, *J* = 7.7 Hz, 2H), 6.80 (dd, *J* = 8.9, 2.1, 2H), 5.92 (s, 1H), 5.41 (s, 2H), 3.75 (s, 3H), 2.29 (s, 3H), 1.52 (s, 6H). ^{13}C-NMR (125 MHz, CDCl$_3$) δ (ppm) = 168.7 (C$_q$), 158.7 (C$_q$), 153.1 (C$_q$), 138.5 (C$_q$), 136.8 (C$_q$), 135.1 (C$_q$), 134.6 (C$_q$), 132.8 (C$_q$), 130 (CH), 128.8 (CH), 128.7 (CH),

128.4 (CH), 128.4 (CH), 127.7 (CH), 127 (CH), 120.4 (CH), 113.4 (CH), 55.2 (CH_3), 53.8 (CH_2), 51.6 (C_q), 27.5 (CH_3), 19.2 (CH_3). IR (ATR): 3294, 2977, 1651, 1512, 1456, 1178, 790, 721, 695, 533 cm^{-1}. MS (EI) m/z (relative intensity): 440 (60) [M^+], 397 (90), 240 (15), 225 (75), 200 (20), 182 (22), 153 (15), 91 (100). HR-MS (EI) *m/z* calculated for $C_{27}H_{28}N_4O_2$ [M^+]: 440.2212; found: 440.2210. The analytical data were in accordance with the data reported in the literature.[11c]

_N_-{1-(1-Benzyl-1_H_-1,2,3-triazol-4-yl)cyclohexyl}-4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxamide (3ba)

The representative procedure A was followed using **1b** (113 mg, 0.3 mmol), 4-iodoanisole (**2a**) (280 mg, 1.2 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5.0 mol %), and AgOAc (55.0 mg, 0.33 mmol). Column chromatography on silica gel (*n*pentane/EtOAc 1/1) yielded **3ba** (136.8 mg, 95%) as a white solid. M.p. = 174-176. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.36-7.29 (m, 3H), 7.26 (dd, *J* = 8.8, 2.0, 2H), 7.24-7.21 (m, 3H), 7.08 (dd, *J* = 10.9, 7.5 Hz, 2H), 6.78 (dd, *J* = 8.8, 2.2 Hz, 2H), 5.46 (s, 2H), 5.44 (s, 1H), 3.78 (s, 3H), 2.26-2.17 (m, 2H), 2.14 (s, 3H), 1.95-1.84 (m, 2H), 1.36-1.24 (m, 3H), 1.24-1.16 (m, 1H), 1.15-1.04 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.9 (C_q), 158.9 (C_q), 151.9 (C_q), 138.6 (C_q), 137.0 (C_q), 135.3 (C_q), 135.0 (C_q), 133.0 (C_q), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 128.4 (CH), 127.7 (CH), 127.2 (CH), 121.9 (CH), 113.6 (CH), 55.3 (CH_3), 53.9 (C_q), 53.8 (CH_2), 34.8 (CH_2), 25.2 (CH_2), 21.3 (CH_2), 21.2 (CH_3). IR (ATR): 3258, 1629, 1514, 1464, 1151, 1048, 959, 846, 720, 458 cm^{-1}. HR-MS (ESI) *m/z* calcd for $C_{30}H_{32}N_4O_2$ [M+Na^+] 503.2423, found 503.2417.

4'-Methoxy-_N_-(2-{1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl}propan-2-yl)-3-methyl-[1,1'-biphenyl]-2-carboxamide (3ca)

The representative procedure A was followed using **1c** (109 mg, 0.3 mmol), 4-iodoanisole (**2a**) (280 mg, 1.2 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5.0 mol %), and AgOAc (55.0 mg, 0.33 mmol). Column chromatography on silica gel (*n*pentane/EtOAc 1/1) yielded **3ca** (126.2 mg, 90%) as a white solid. M.p. = 127-128 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.30 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.23 (dd, *J* = 7.7 Hz, 1H), 7.19-7.14 (m, 3H), 7.09 (t, *J* = 7.2 Hz, 2H), 6.85 (dd, *J* = 8.7, 2.0 Hz, 2H), 6.80 (dd, *J* = 8.7, 2.0 Hz, 2H), 5.94 (s, 1H), 5.34 (s, 2H), 3.76 (s, 6H), 2.29 (s, 3H), 1.51 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.8 (C_q), 159.6 (C_q), 158.8 (C_q), 153.1 (C_q), 138.6 (C_q), 136.8 (C_q), 135.2 (C_q), 132.8 (C_q), 129.9 (CH), 129.3 (CH), 128.7 (CH), 128.4 (CH), 127.1 (CH), 126.6 (C_q), 120.1 (CH), 114.3 (CH), 113.4 (CH), 55.2 (CH_3), 53.4 (CH_2), 51.6 (C_q), 27.3 (CH_3), 19.1 (CH_3), 19.1 (CH_3). IR (ATR): 3258, 2837, 1637, 1611, 1513, 1459, 1244, 1178, 833, 665 cm^{-1}. HR-MS (ESI) *m/z* calcd for $C_{28}H_{31}N_4O_3$ [M+H^+] 471.2396, found 471.2391.

_N_-(2-{1-(4-Fluorophenyl)-1_H_-1,2,3-triazol-4-yl}propan-2-yl)-4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxamide (3da)

The representative procedure A was followed using **1d** (101 mg, 0.3 mmol), 4-iodoanisole (**2a**) (280 mg, 1.2 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5.0 mol %), and AgOAc (55.0 mg, 0.33 mmol). Column chromatography on silica gel (*n*pentane/EtOAc 1/1) yielded **3da** (123.5 mg, 93%) as a white solid. M.p. = 170-172 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.67 (s, 1H), 7.66-7.62 (m, 2H), 7.32 (dd, *J* = 8.7, 2.0 Hz, 2H), 7.26 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.21-7.17 (m, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.81 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.86 (s, 1H), 3.72 (s, 3H), 2.37 (s, 3H), 1.64 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 169.0 (C_q), 162.3 (C_q, $J_{C\text{-}F}$ = 248.5 Hz), 158.9 (C_q), 153.4 (C_q), 138.8 (C_q), 136.8 (C_q), 135.2 (C_q), 133.4 (C_q,$J_{C\text{-}F}$ = 3.1 Hz), 132.9 (C_q), 130.0 (CH), 128.9 (CH), 128.7 (CH), 127.3 (CH), 122.5 (CH,$J_{C\text{-}F}$ = 8.5 Hz), 119.1 (CH), 116.5 (CH,$J_{C\text{-}F}$ = 23 Hz), 113.5 (CH), 55.2 (CH_3), 51.7 (C_q), 27.7 (CH_3), 19.3 (CH_3). ^{19}F-NMR (283 MHz, $CDCl_3$): δ = -112.40 (d, *J* = 4.5 Hz). IR (ATR): 3258, 1629, 1514, 1248, 1221, 1179, 1039, 817, 787, 538 cm^{-1}. HR-MS (ESI) *m/z* calcd for $C_{26}H_{25}FN_4O_2$ [M+H^+] 445.2040, found 445.2034.

_N_-{2-(1-_n_Butyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl}-4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxamide (3ea)

The representative procedure A was followed using **1e** (150 mg, 0.5 mmol), 4-iodoanisole (**2a**) (468 mg, 2.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), and AgOAc (91.8 mg, 0.55 mmol). Column chromatography on silica gel (*n*-pentane/EtOAc 1/1) yielded **3ea** (194.6 mg, 96%) as a white solid. M.p. = 108-109 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 8.6, 2.0 Hz, 2H), 7.24 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.19 (s, 1H), 7.13-7.09 (m, 2H), 6.86 (dd, *J* = 8.6, 2.1 Hz, 2H), 5.94 (s, 1H), 4.23 (t, *J* = 7.3 Hz, 2H), 3.80 (s, 3H), 2.33 (s, 3H), 1.84-1.78 (m, 2H), 1.56 (s, 6H), 1.35-1.27 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.8 (C_q), 158.9 (C_q), 152.8 (C_q), 138.7 (C_q), 137.0 (C_q), 135.2 (C_q), 133.0 (C_q), 130.1 (CH), 128.8 (CH), 128.5 (CH), 127.1 (CH), 120.2 (CH), 113.5 (CH), 55.2 (CH_3), 51.7 (C_q), 49.8 (CH_2), 32.2 (CH_2), 27.5 (CH_3), 19.6 (CH_2), 19.2 (CH_3), 13.4 (CH_3). IR (ATR): 3258, 2959, 1610, 1539, 1512, 1458, 1244, 1178, 1031, 656 cm^{-1}. MS (EI) *m/z* (relative intensity): 406 (30) [M^+], 363 (55), 240 (15), 225 (55), 224 (30), 182 (15), 166 (25), 58 (20), 57 (30). HR-MS (EI) *m/z* calcd for $C_{24}H_{30}N_4O_2$ [M^+] 406.2369, found 406.2361.

_N_-(2-[1-Benzyl-1_H_-1,2,3-triazol-4-yl]propan-2-yl)-3-methyl-[1,1'-biphenyl]-2-carboxamide (3ab)

The representative procedure A was followed using **1a** (167 mg, 0.50 mmol), iodobenzene (**2b**) (408 mg, 2.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (npentane/EtOAc 3:1 → 1:1) yielded **3ab** (188 mg, 92%) as a white solid. M.p.: 177–178 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40–7.32 (m, 5H), 7.30–7.18 (m, 6H), 7.17–7.10 (m, 3H), 5.83 (s, 1H), 5.43 (s, 2H), 2.30 (s, 3H), 1.49 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.7 (C_q), 153.5 (C_q), 140.7 (C_q), 139.2 (C_q), 137.0 (C_q), 135.5 (C_q), 134.8 (C_q), 129.3 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 127.3 (CH), 127.2 (CH), 120.5 (CH), 53.9 (CH_2), 51.6 (C_q), 27.3 (CH_3), 19.2 (CH_3). IR (ATR): 3314, 2924, 1635, 1539, 1309, 1198, 1053, 760, 730, 632. MS (EI) m/z (relative intensity): 410 (35), 382 (15), 367 (85), 200 (16), 195 (80), 165 (42), 152 (35), 98 (24), 91 (100), 57 (22), 43 (52). HR-MS (EI) *m/z* calculated for $C_{26}H_{26}N_4O$ [M^+]: 410.2107; found: 410.2119. The analytical data were in accordance with the data reported in the literature.[11c]

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-4'-fluoro-3-methyl-[1,1'-biphenyl]-2- carboxamide (3ac)**

The representative procedure A was followed using **1a** (167 mg, 0.50 mmol), 1-fluoro-4-iodobenzene (**2c**) (444 mg, 2.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ac** (150 mg, 70%) as a white solid. M.p.: 157–158 °C. 61 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 5H), 7.26–7.18 (m, 4H), 7.17–7.05 (m, 2H), 6.99–6.87 (m, 2H), 6.03 (s, 1H), 5.42 (s, 2H), 2.30 (s, 3H), 1.52 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.6 (C_q), 162.3 (C_q, $J_{C\text{-}F}$ = 246 Hz), 153.4 (C_q), 138.1 (C_q), 136.5 (C_q, $J_{C\text{-}F}$ = 3 Hz), 136.5 (C_q), 135.4 (C_q), 134.7 (C_q), 130.6 (CH, $J_{C\text{-}F}$ = 8 Hz), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.7 (CH), 128.0 (CH), 127.1 (CH), 120.2 (CH), 114.9 (CH, $J_{C\text{-}F}$ = 21 Hz), 54.1 (CH_2), 51.8 (C_q), 27.4 (CH_3), 19.2 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -(115.6-115.7) (m). IR (ATR): 3289, 2980, 1634, 1539, 1508, 1218, 1194, 1051, 938, 529. MS (EI) *m/z* (relative intensity): 428 (40) [M^+], 385 (100), 213 (80), 212 (15), 183 (25), 165 (30), 91 (80), 43 (27). HRMS (EI) *m/z* calculated for $C_{26}H_{25}FN_4O^+$: 428.2012; found: 428.2020. The analytical data were in accordance with the data reported in the literature.[11c]

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-3-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (3ad)**

The representative procedure A was followed using **1a** (167 mg, 0.50 mmol), 1-iodo-4-(trifluoromethyl)benzene (**2d**) (544 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*-pentane/EtOAc 3:1 → 1:1) yielded **3ad** (217 mg, 91%) as a white solid. M.p. = 183–185 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.55 – 7.47 (m, 4H), 7.42–7.15 (m, 8H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.10 (s, 1H), 5.43 (s, 2H), 2.32 (s, 3H), 1.50 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.3 (C_q), 153.3 (C_q), 144.2 (C_q), 137.7 (C_q), 136.9 (C_q), 135.5 (C_q), 134.5 (C_q), 139.9 (CH), 129.4 (C_q, $J_{C\text{-}F}$ = 33.3 Hz), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 126.9 (CH), 124.9 (CH, $J_{C\text{-}F}$ = 3.3 Hz), 124.2 (C_q, $J_{C\text{-}F}$ = 272.0 Hz), 120.2 (CH), 54.0 (CH_2), 51.7 (C_q), 27.0 (CH_3), 19.1 (CH_3). ^{19}F-NMR (282 MHz, CDCl3) δ = -62.35 (s). IR (ATR): 3283, 2978, 1635, 1189, 1154, 1062, 848, 790, 716, 608 cm^{-1}. MS (EI) *m/z* (relative intensity): 478 (30) [M^+], 450 (18), 435 (85), 263 (75), 215 (22), 165 (30), 91 (100), 65 (10), 43 (15). HR-MS (EI) *m/z* calculated for $C_{27}H_{25}F_3N_4O$ [M^+]: 478.1980; found: 478.1967.

***N*-{2-[1-Benzyl-1*H*-1,2,3-triazol-4-yl]propan-2-yl}-3'-methoxy-3-methyl-[1,1'-biphenyl]-2- carboxamide (3ae)**

The representative procedure A was followed using **1a** (167 mg, 0.50 mmol), 3-iodoanisole (**2e**) (487 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ae** (185 mg, 84%) as a dark oil. ^{1}H-NMR (600 MHz, $CDCl_3$) δ = 7.35–7.30 (m, 3H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.22–7.12 (m, 6H), 6.96–6.94 (m, 2H), 6.82–6.80 (m, 1H), 5.90 (s, 1H), 5.42 (s, 2H), 3.73 (s, 3H), 2.30 (s, 3H), 1.50 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.7 (C_q), 159.2 (C_q), 153.4 (C_q), 142.0 (C_q), 139.0 (C_q), 136.9 (C_q), 135.4 (C_q), 134.8 (C_q), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.6 (CH), 127.8 (CH), 126.9 (CH), 121.2 (CH), 120.4 (CH), 114.0 (CH), 113.6 (CH), 55.1 (CH_3), 53.8 (CH_2), 51.6 (C_q), 27.2 (CH_3), 19.1 (CH_3). IR (ATR): 3304, 2836, 1652, 1497, 1456, 1299, 1222, 1046, 722, 698 cm^{-1}. MS (EI) *m/z* (relative intensity): 440 (10) [M^+], 397 (85), 240 (10), 225 (55), 201 (22), 182 (20), 165 (15), 153 (15), 91 (100), 65 (8). HR-MS (EI) *m/z* calculated for $C_{27}H_{28}N_4O_2$ [M^+]: 440.2212; found: 440.2214. The analytical data were in accordance with the data reported in the literature.[11c]

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-2'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxamide (3af)**

The representative procedure A was followed using **1a** (167 mg, 0.50 mmol), 2-iodoanisole (**2f**) (487 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3af** (176 mg, 80%) as a colorless solid. M.p. = 173–174 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ = 7.36–7.30 (m, 3H), 7.23 (dd, *J* = 7.6 Hz, 1H), 7.19–7.11 (m, 5H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.88 (s, 1H), 6.83 (ddd, *J* = 7.4, 1.0 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.30 (s, 1H), 5.37 (s, 2H), 3.62 (s, 3H), 2.31 (s, 3H), 1.45 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.1 (C_q), 156.1 (C_q), 153.1 (C_q), 137.4 (C_q), 135.3 (C_q), 134.9 (C_q), 134.7 (C_q), 130.9 (CH), 129.6 (C_q), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 120.3 (CH), 120.1 (CH), 110.3 (CH), 55.2 (CH_3), 53.8 (CH_2), 51.4 (C_q), 27.5 (CH_3), 19.3 (CH_3). IR (ATR): 3391, 3116, 3079, 1646, 1515, 1455, 1228, 757, 729, 477 cm^{-1}. MS (EI*) m/z* (relative intensity): 440 (10) [M^+], 397 (80), 225 (60), 210 (53), 201 (85), 181 (30), 165 (12), 152 (10), 91 (100), 65 (10). HR-MS (EI*) m/z* calculated for $C_{27}H_{28}N_4O_2$ [M^+]: 440.2212; found: 440.2211.

Methyl 2'-{(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}carbamoyl)-3'-methyl-[1,1'-biphenyl]-4-carboxylate (3ag)

The representative procedure A was followed using **1a** (167 mg, 0.50 mmol), methyl 4-iodobenzoate (**2g**) (524 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ag** (227 mg, 95%) as a yellow-orange solid. M.p. = 136–138 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.95 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.46 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.40–7.08 (m, 9H), 6.07 (s, 1H), 5.42 (s, 2H), 3.88 (s, 3H), 2.30 (s, 3H), 1.49 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.5 (C_q), 167.0 (C_q), 153.3 (C_q), 145.3 (C_q), 138.0 (C_q), 136.8 (C_q), 135.5 (C_q), 134.7 (C_q), 129.9 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.9 (C_q), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.0 (CH), 120.3 (CH), 53.9 (CH_2), 52.0 (CH_3), 51.6 (C_q), 27.2 (CH_3), 19.0 (CH_3). IR (ATR): 3291, 2948, 1654, 1518, 1455, 1275, 1181, 1048, 768, 705 cm^{-1}. MS (EI) *m/z* (relative intensity): 468 (32) [M^+], 425 (100), 253 (18), 209 (25), 194 (18), 165 (40), 91 (95), 59 (8). HR-MS (EI) *m/z* calculated for $C_{28}H_{28}N_4O_3$ [M^+]: 468.2161; found: 468.2163.

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl}propan-2-yl)-4'-cyano-3-methyl-[1,1'-biphenyl]-2-carboxamide (3ah)**

Representative procedure A was followed using **1a** (167 mg, 0.50 mmol), 4-iodobenzonitrile (**2h**) (458 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ah** (205 mg, 94%) as a yellow-orange solid. M.p. = 143–145 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 8.9, 2.2 Hz, 4H), 7.39–7.18 (m, 8H), 7.11–7.08 (m, 1H), 6.19 (s, 1H), 5.45 (s, 2H), 2.32 (s, 3H), 1.52 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.3 (C_q), 153.4 (C_q), 145.3 (C_q), 137.3 (C_q), 136.9 (C_q), 135.7 (C_q), 134.6 (C_q), 131.9 (CH), 130.4 (CH), 129.7 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.1 (CH), 126.8 (CH), 120.1 (CH), 118.9 (C_q), 111.0 (C_q), 54.1 (CH_2), 51.7 (C_q), 27.2 (CH_3), 19.1 (CH_3). IR (ATR): 3283, 2228, 1636, 1540, 1457, 1311, 1050, 848, 722, 666 cm^{-1}. MS (EI) *m/z* (relative intensity): 435 (30), 392 (70), 220 (65), 190 (22), 177 (12), 165 (25), 98 (10), 91 (100), 65 (65). HR-MS (EI) *m/z* calculated for $C_{27}H_{25}N_5O$ [M$^+$]: 435.2059; found: 435.2062.

4'-Acetyl-*N*-{2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-3-methyl-[1,1'-biphenyl]-2-carboxamide (3ai)

The representative procedure A was followed using **1a** (167 mg, 0.50 mmol), 4-iodoacetophenone (**2i**) (492 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ai** (210 mg, 89%) as a yellow solid. M.p. = 130–132 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.84 (dd, *J* = 8.2, 2.0 Hz, 2H), 7.48 (dd, *J* = 8.1, 2.3 Hz, 2H), 7.39–7.09 (m, 9H), 6.07 (s, 1H), 5.43 (s, 2H), 2.56 (s, 3H), 2.31 (s, 3H), 1.50 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 198.0 (C_q), 168.5 (C_q), 153.1 (C_q), 145.4 (C_q), 138.0 (C_q), 136.8 (C_q), 135.9 (C_q), 135.6 (C_q), 134.7 (C_q), 123.0 (CH), 129.1 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 127.0 (CH), 120.5 (CH), 54.0 (CH_2), 51.6 (C_q), 27.2 (CH_3), 26.6 (CH_3), 19.1 (CH_3). IR (ATR): 2977, 1636, 1538, 1359, 1270, 1184, 1050, 603 cm^{-1}. MS (EI) *m/z* (relative intensity): 452 (42) [M$^+$], 424 (22), 409 (100), 237 (20), 195 (50), 165 (20), 91 (90), 43 (50). HR-MS (EI) *m/z* calculated for $C_{28}H_{28}N_4O_2$ [M$^+$]: 452.2212; found: 452.2201.

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-3-(4-methoxyphenyl)-2-naphthamide (3ja)**

The representative procedure A was followed using **1j** (111 mg, 0.30 mmol), 4-iodoanisole (**2a**) (280 mg, 1.2 mmol), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 5.0 mol %) and AgOAc (55 mg, 0.33 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ja** (140 mg, 98%) as a white solid. M.p. = 202-203 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 8.09 (s, 1H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.50-7.43 (m, 2H), 7.35 (s, 1H), 7.34-7.28 (m, 5H), 7.23-7.19 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.19 (s, 1H), 5.41 (s, 2H), 3.77 (s, 3H), 1.61 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.2 (C_q), 159.0 (C_q), 153.1 (C_q), 136.5 (C_q), 134.7 (C_q), 134.4 (C_q), 133.5 (C_q), 132.5 (C_q), 131.5 (C_q), 130 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 126.3 (CH), 120.5 (CH), 113.7 (CH), 55.2 (CH_3), 53.8 (CH_2), 51.5 (C_q), 27.3 (CH_3). IR (ATR): 3281, 1630, 1545, 1244, 1207, 1176, 1050, 820, 718, 527 cm^{-1}. MS (EI) *m/z* (relative intensity): 476 (43) [M$^+$], 433 (100), 276 (25), 261 (85), 218 (22), 189 (32), 91 (66). HR-MS (EI) *m/z* calcd for $C_{30}H_{28}N_4O_2^+$[M$^+$] 476.2212, found 476.2193. The analytical data were in accordance with the data reported in the literature.[11c]

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-3-chloro-4'-methoxy-[1,1'-biphenyl]-2-carboxamide (3ka)**

The representative procedure A was followed using **1k** (177 mg, 0.50 mmol), 4-iodoanisole (**2a**) (468 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ka** (190 mg, 82%) as a white solid. M.p. = 137-139 °C. ^{1}H-NMR (600 MHz, C_6D_6): δ = 7.28-7.21 (m, 5H), 7.21 – 7.20 (m, 1H), 7.19-7.17 (m, 2H), 7.14-7.11 (m, 2H), 7.10 (dd, *J* = 7.0, 1.8 Hz, 2H), 6.73 (dd, *J* = 8.5, 1.9 Hz), 5.97 (s, 1H), 5.33 (s, 2H), 3.68 (s, 3H), 1.48 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 165.8 (C_q), 159.3 (C_q), 153.0 (C_q), 141.1 (C_q), 136.1 (C_q), 134.6 (C_q), 131.5 (C_q), 131.3 (C_q), 130.0 (CH), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 120.6 (CH), 113.6 (CH), 55.3 (CH_3), 53.9 (CH_2), 52.3 (C_q), 27.6 (CH_3) . IR (ATR): 3258, 1637, 1561, 1455, 1046, 840, 731, 704, 693, 583 cm^{-1}. MS (EI) *m/z* (relative intensity): 460 (15) [M$^+$], 432 (15), 419 (30), 417 (80), 247 (15), 245 (50), 210 (20), 139 (25), 91 (100). HR-MS (ESI) *m/z* calcd for $C_{26}H_{25}ClN_4O_2$ [M+H$^+$] 461.1744, found 461.1739.

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-3-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carboxamide (3la)**

The representative procedure A was followed using **1l** (169 mg, 0.50 mmol), 4-iodoanisole (**2a**) (468 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3la** (185 mg, 84%) as a white solid. M.p. = 144-146 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.36-7.30 (m, 6H), 7.28 (s, 1H), 7.23-7.20 (m, 2H), 7.09 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.00 (dd, *J* = 8.7, 8.2, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.7, 2 Hz, 2H), 6.18 (s, 1H), 5.43 (s, 2H), 3.77 (s, 3H), 1.61 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 164.0 (C_q), 159.3 (C_q,d, $J_{C\text{-}F}$ = 247.8 Hz), 159.3 (C_q), 153.0 (C_q), 141.3 (C_q, d, $J_{C\text{-}F}$ = 3.6 Hz), 134.6 (C_q), 131.2 (C_q,d, $J_{C\text{-}F}$ = 2.3 Hz), 130.1 (CH, d, $J_{C\text{-}F}$ = 8.9 Hz), 129.7 (CH), 128.9 (CH), 128.4 (CH), 127.7 (CH), 125.3 (CH, d, $J_{C\text{-}F}$ = 3.0 Hz), 125.1 (C_q, d, $J_{C\text{-}F}$ = 18.0 Hz), 120.5 (C_q), 113.9 (CH, d, $J_{C\text{-}F}$ = 22.0 Hz), 113.6 (CH), 55.2 (CH_3), 53.8 (CH_2), 52.2 (C_q), 27.5 (CH_3). ^{19}F-NMR (283 MHz, $CDCl_3$): δ = -116.64 (dd, *J* = 9.1, 5.9 Hz). IR (ATR): 3258, 1608, 1581, 1450, 1235, 1027, 894, 815, 795, 486 cm^{-1}. MS (EI) *m/z* (relative intensity): 444 (30) [M$^+$], 416 (20), 402 (30), 401 (100), 229 (50), 186 (30), 91 (80) . HR-MS (ESI) *m/z* calcd for $C_{26}H_{25}FN_4O_2$ [M+H$^+$] 445.2040, found 445.2034.

***N*-{2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}-4,4'-dimethyl-[1,1'-biphenyl]-2-carboxamide (3nj)**

The representative procedure A was followed using **1n** (167 mg, 0.50 mmol), 1-iod-4-methylbenzene (**2j**) (436 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*-pentane/EtOAc 3:1 → 1:1) yielded **3nj** (189 mg, 95%) as a

white solid. M.p. = 170-172 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.44-7.40 (m, 1H), 7.39-7.31 (m, 3H), 7.30 (s, 1H), 7.25-7.15 (m, 6H), 7.12-7.06 (m, 2H), 5.78 (s, 1H), 5.44 (s, 2H), 2.36 (s, 3H), 2.33 (s, 3H), 1.52 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 168.5 (C_q), 153.2 (C_q), 137.3 (C_q), 137.1 (C_q), 137.1 (C_q), 136.7 (C_q), 135.9 (C_q), 134.8 (C_q), 130.6 (CH), 130.0 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 120.6 (CH), 53.9 (CH_2), 51.5 (C_q), 27.3 (CH_3), 21.1 (CH_3), 20.8 (CH_3). IR (ATR): 3258, 1635, 1544, 1380, 1321, 1046, 813, 732, 693, 497 cm^{-1}. MS (EI) *m/z* (relative intensity): 424 (15) [M$^+$], 396 (15), 382 (30), 381 (100), 209 (65), 166 (35), 165 (45), 91 (75). HR-MS (EI) *m/z* calcd for $C_{27}H_{28}N_4O$ [M$^+$] 424.2263, found 424.2250.

_N_-{2-(1-Benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl}-4'-methoxy-4-methyl-[1,1'-biphenyl]-2-carboxamide (3na)

The representative procedure A was followed using **1n** (167 mg, 0.50 mmol), 4-iodoanisole (**2a**) (436 mg, 2.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3na** (185 mg, 84%) as a colorless solid. M.p. = 166 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.44–7.23 (m, 4H), 7.32 (s, 1H), 7.29-7.16 (m, 6H), 6.84 (dd, *J* = 8.2, 2.0 Hz, 2H) 5.80 (s, 1H), 5.47 (s, 2H), 3.80 (s, 3H), 2.38 (s, 3H), 1.56 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.5 (C_q), 159.0 (C_q), 153.1 (C_q), 136.9 (C_q), 136.3 (C_q), 135.8 (C_q), 134.7 (C_q), 132.5 (C_q), 130.6 (CH), 130.0 (CH), 123.0 (CH), 129.1 (CH), 129.0 (CH), 128.5 (CH), 127.9 (CH), 120.5 (CH), 113.8 (CH), 55.4 (CH_3), 54.0 (CH_2), 51.6 (C_q), 27.5 (CH_3), 21.0 (CH_3). IR (ATR): 3294, 2995, 1609, 1458, 1242, 1174, 1044, 823, 781, 507 cm^{-1}. MS (EI) *m/z* (relative intensity): 440 (30) [M$^+$], 397 (100), 240 (12), 225 (60), 182 (20), 153 (15), 91 (80), 65 (10). HR-MS (EI) *m/z* calculated for $C_{27}H_{28}N_4O_2$ [M$^+$]: 440.2212; found: 440.2210.

Methyl 2'-[{2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl}carbamoyl]-4'-methyl-[1,1'-biphenyl]-4-carboxylate (3ng)

The representative procedure A was followed using **1n** (167 mg, 0.50 mmol), methyl-4-iodobenzoate (**2g**) (524 mg, 2.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ng** (193 mg, 82%) as a colorless solid. M.p. = 173–175 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.97 (dd, *J* = 8.5, 1.9 Hz, 2H), 7.44-7.31 (m, 6H), 7.27 (s, 1H) 7.25-7.19 (m, 4H), 6.01 (s, 1H), 5.45 (s, 2H), 3.91 (s, 3H), 2.38 (s, 3H), 1.57 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 168.3 (C_q), 166.7 (C_q), 153.1 (C_q), 145.0 (C_q), 138.0 (C_q), 136.3 (C_q), 135.7 (C_q), 134.6 (C_q), 130.6 (CH), 129.9 (CH), 129.5 (CH), 129.0 (CH), 128.8 (C_q), 128.8 (2CH), 128.6 (CH), 127.9 (CH), 120.3 (CH), 54.1 (CH_2), 52.1 (CH_3), 51.8 (C_q), 27.4 (CH_3), 21.0 (CH_3). IR (ATR): 3269, 1715, 1659, 1526, 1278, 1113, 826, 721, 535 cm^{-1}. MS (EI) *m/z* (relative intensity): 468 (5), 440 (30), 425 (100), 253 (15), 209 (25), 165 (30), 98 (12), 91 (65), 43 (10). HR-MS (EI) *m/z* calculated for $C_{28}H_{28}N_4O_3$ [M$^+$]: 468.2161; found: 468.2153.

4'-Acetyl-_N_-{2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl}-4-methyl-[1,1'-biphenyl]-2-carboxamide (3ni)

The representative procedure A was followed using **1n** (167 mg, 0.50 mmol), 4-iodoacetophenone (**2i**) (492 mg, 2.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 0.55 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 1:1) yielded **3ni** (185 mg, 95%) as a colorless solid. M.p. = 141-143 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34 (s_{br}, 1H), 7.32 (s, 1H), 7.31-7.24 (m, 3H), 7.22-7.15 (m, 4H), 6.23 (s, 1H), 5.39 (s, 2H), 2.51 (s, 3H), 2.32 (s, 3H), 1.55 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 197.5 (C_q), 168.3 (C_q), 152.9 (C_q), 144.9 (C_q), 137.8 (C_q), 136.3 (C_q), 135.6 (C_q), 135.6 (C_q), 134.5 (C_q), 130.5 (CH), 129.7 (CH), 128.8 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.7 (CH), 120.4 (CH), 53.76 (C_q), 51.49 (CH_2), 27.18 (CH_3), 26.44 (CH_3), 20.75 (CH_3) . IR (ATR): 3260, 1671, 1637, 1604, 1554, 1221, 1185, 1005, 855, 502 cm^{-1}. MS (EI) *m/z* (relative intensity): 452 (5), 424 (30), 410 (35), 409 (100), 195 (60), 91 (85), 65 (10), 43 (50). HR-MS (EI) *m/z* calcd for $C_{28}H_{28}N_4O_2$ 452.2212 [M$^+$], found 452.2205.

_N_-{2-(1-Benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl}-3,4'-dimethyl-[1,1'-biphenyl]-2-carboxamide (3aj)

The representative procedure B was followed using **1a** (167 mg, 0.50 mmol), 4-methyl-1-iodobenzene (**2j**) (218 mg, 1.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), PivOH (15.3 mg, 0.15 mmol) and $KHCO_3$ (100 mg, 1.00 mmol). Purification by column chromatography on silica gel (n-pentane /EtOAc 3:1 → 2:1 → 1:1) yielded **3aj** (146 mg, 69%) as a white solid. M. p. = 132–133 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 3H), 7.28–7.15 (m, 6H), 7.16–6.95 (m, 4H), 5.90 (s, 1H), 5.41 (s, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 1.51 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 168.7 (C_q), 153.3 (C_q), 139 (C_q), 137.6 (C_q), 136.8 (C_q), 135.3 (C_q), 134.7 (C_q), 128.9 (CH), 128.9 (CH), 128.7 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 120.5 (CH), 53.9 (C_q), 51.6 (CH_2), 27.3 (CH_3), 21.0 (CH_3), 19.2 (CH_3). IR (neat): 3292, 1633, 1542, 1461, 1309, 1216, 1050, 826, 723, 649 cm^{-1}. MS (EI) *m/z* (relative intensity): 424 (35) [M$^+$], 381 (92), 209 (80), 165 (53), 91 (100). HR-MS (EI) *m/z* calcd for $C_{27}H_{28}N_4O^+$[M$^+$] 424.2263, found 424.2252. The analytical data were in accordance with the data reported in the literature.[11c]

_N_-{2-(1-Benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl}-4'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (3ma)

The representative procedure B was followed using **1m** (194 mg, 0.50 mmol), 4-iodoanisole (**2a**) (234 mg, 1.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol %), PivOH (15.3 mg, 0.15 mmol) and $KHCO_3$ (100 mg, 1.00 mmol). Purification by column chromatography on silica gel (*n*pentane /EtOAc 3:1 → 2:1 → 1:1) yielded **3ma** (226 mg, 91%) as a white solid. M.p. = 164–165 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ = 7.85 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.37-7.33 (m, 3H), 7.32 (s, 1H), 7.27 (dd, *J* = 8.7, 2.1 Hz, 2H), 7.24-7.22 (m, 2H), 6.86 (dd, *J* = 8.6, 2.2 Hz, 2H), 5.98 (s, 1H), 5.45 (s, 2H), 3.79 (s, 3H), 1.56 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 167.1 (C_q), 159.9 (C_q), 152.9 (C_q), 136.7 (C_q), 142.8 (C_q) 134.7 (C_q), 131.1 (C_q), 130.7 (CH), 130.0 (CH), 129.4 (C_q, q, J_{C-F} = 33.0 Hz) , 129.1 (CH), 128.7 (CH), 128.0 (CH), 126.5 (CH, q, J_{C-F} = 4.0 Hz), 125.8 (CH,

q, J_{C-F} = 3.9 Hz) , 123.8 (C_q, q, J_{C-F} = 272.3 Hz) , 120.5 (CH), 114.1 (CH), 55.4 (CH_3), 54.1 (CH_2), 51.8 (C_q), 27.3 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -62.54 (s). IR (ATR): 3278, 2983, 1634, 1338, 1302, 1255, 1172, 1150, 1120, 720 cm^{-1}. MS (EI) *m/z* (relative intensity): 494 (13) [M^+], 466 (20), 451 (90), 279 (45), 236 (15), 91 (100). HRMS (EI) *m/z* calculated for $C_{27}H_{25}F_3N_4O_2$ [M^+]: 494.1930; found: 494.1934.

Methyl 2'-[{2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl}carbamoyl]-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate (3mg)

The representative procedure A was followed using **1m** (194 mg, 0.50 mmol), methyl 4-iodobenzoate (**2g**) (524 mg, 2.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %) and AgOAc (91.8 mg, 2.00 mmol). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 2:1 → 1:1) yielded **3mg** (242 mg, 93%) as a colorless solid. M.p. = 172–173 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.02 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.84–7.83 (m, 1H), 7.72–7.68 (m, 1H), 7.48–7.42 (m, 3H), 7.38–7.32 (m, 3H), 7.25–7.21 (m, 3H), 6.18 (s, 1H), 5.46 (s, 2H), 3.92 (s, 3H), 1.57 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 166.7 (C_q), 166.5 (C_q), 152.8 (C_q), 143.4 (C_q), 142.1 (C_q), 137.1 (C_q), 134.4 (C_q), 130.5 (CH), 130.3 (C_q, J_{C-F} = 33.0 Hz), 129.8 (CH), 129.7 (CH), 129.0 (CH), 128.7 (CH), 128.7 (CH), 128.0 (CH), 126.6 (CH, J_{C-F} = 4.0 Hz), 125.3 (CH, J_{C-F} = 4.0 Hz) , 123.5 (C_q, J_{C-F} = 272.0 Hz), 120.2 (CH), 54.2 (CH_2), 52.3 (CH_3), 52.1 (C_q), 27.4 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$) δ (ppm) = -62.66 (s). IR (ATR): 3345, 3129, 1707, 1667, 1533, 1336, 1131, 1102, 1079, 727 cm^{-1}. MS (EI) *m/z* (relative intensity): 494 (35), 479 (100), 263 (25), 248 (12), 98 (10), 91 (100), 59 (20). HR-MS (EI) *m/z* calculated for $C_{28}H_{25}F_3N_4O$ [M^+]: 522.1879; found: 522.1883.

4'-Acetyl-*N*-{2-(1-benzyl-1*H*-1,2,3-triazol-4-yl}propan-2-yl)-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (3mi)

The representative procedure B was followed using **1m** (194 mg, 0.50 mmol), 4-iodoacetophenone (**2i**) (246 mg, 1.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), PivOH (15.3 mg, 0.15 mmol, 30 mol %) and $KHCO_3$ (100 mg, 1.0 mmol, 2.0 equiv). Purification by column chromatography on silica gel (*n*pentane/EtOAc 3:1 → 2:1 → 1:1) yielded **3mi** (228 mg, 90 %) as a colorless solid. M.p. = 154–155 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.90 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.83 (s, 1H), 7.72–7.67 (m, 1H), 7.49–7.41 (m, 3H), 7.38–7.30 (m, 4H), 7.24–7.19 (m, 2H), 6.29 (s, 1H), 5.45 (s, 2H), 2.58 (s, 3H), 1.58 (s, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 197.5 (C_q), 166.9 (C_q), 152.8 (C_q), 143.5 (C_q), 142.1 (C_q), 137.2 (C_q), 136.6 (C_q), 134.5 (C_q), 130.6 (CH), 130.3 (C_q, J_{C-F} = 33.1 Hz), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 126.6 (CH, J_{C-F} = 4.2 Hz), 125.3 (CH, J_{C-F} = 4.1 Hz) , 123.6 (C_q, J_{C-F} = 273.1 Hz), 120.4 (CH), 54.1 (CH_2), 52.0 (C_q), 27.3 (CH_3), 26.7 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$) δ = -62.65 (s). IR (ATR): 3268, 2981, 1633, 1339, 1291, 1262, 1175, 1083, 719, 596 cm^{-1}. MS (EI) *m/z* (relative intensity): 506 (5), 478 (30), 463 (80), 249 (18), 98 (10), 91 (100), 65 (8), 43 (60). HRMS (EI) *m/z* calculated for $C_{28}H_{25}F_3N_4O_2$ [M^+]: 506.1930; found: 506.1919.

Traceless Removal of the TAM Group

Aqueous HCl (37%, 5.0 mL) was added to **3mi** (0.126 g, 0.25 mmol) in a pressure tube. The mixture was stirred at 140 °C for 12 h. At ambient temperature, H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined and washed with NaOH (2M, 3 × 20 mL). The combined aqueous layer was acidified with 2M HCl until a pH of 2, and the solution was extracted with CH_2Cl_2 (5 × 100 mL). The organic extracts were dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give 4'-acetyl-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid **4mi** (55 mg, 71 %) as a white solid. M. p. = 94-96 °C. ^{1}H-NMR (300 MHz, CDCl3): δ = 8.30 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.87-7.84 (m, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.44-7.41 (m, 2H), 2.65 (s, 3H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ = -62.78. ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 197.9 (C_q), 170.7 (C_q), 145.9 (C_q), 144.6 (C_q), 136.4 (C_q), 131.7 (CH), 130.4 (C_q, J_{C-F} = 33.7 Hz), 129.7 (C_q), 128.8 (CH, J_{C-F} = 3.4 Hz), 128.6 (CH), 128.3 (CH), 128.1 (CH, J_{C-F} = 3.8 Hz), 123.4 (C_q, J_{C-F} = 270.0 Hz), 26.6 (CH_3). IR (ATR): 1697, 1604, 1328, 1267, 1172, 1126, 1084, 830, 606 cm^{-1}. HRMS *m/z* calculated for $C_{16}H_{11}F_3O_3$ [M+H$^+$] 309.0739, found 309.0734 [M+H$^+$].

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FULL PAPER

C–H Activation

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Page No. – Page No.

Triazole-Assisted Palladium-Catalyzed C−H Arylation of Amides

Palladium catalyzed C − H arylations of benzamides were accomplished by removable triazole amines (TAM) with ample substrate scope under silver-free reaction conditions.