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Carboxylate-assisted ruthenium(II)-catalyzed C–H arylations of 5-aryl tetrazoles: step-economical access to Valsartan

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ABSTRACT

Carboxylate assistance was key to success for highly efficient ruthenium-catalyzed direct *ortho*-arylations of tetrazolyl-substituted arenes with aryl halides and triflates in the absence of phosphine ligands. Thus, ruthenium(II) biscarboxylates allowed for C–H bond functionalizations with excellent chemo- and site-selectivities, which set the stage for an atom- and step-economical access to key angiotensin-II-receptor blockers. Mechanistic studies revealed the C–H bond metalation to be reversible, and were suggestive of a rate-determining reductive elimination.

1. Introduction

Hypertension is one of the most prevalent diseases in developed countries, and nonpeptidic angiotensin-II-receptor blockers (ARBs), such as Valsartan or Losartan (Fig. 1), have emerged as highly effective antihypertensives.[1] As a consequence, these ARBs are produced in more than 1000 t per year worldwide for clinical treatment.

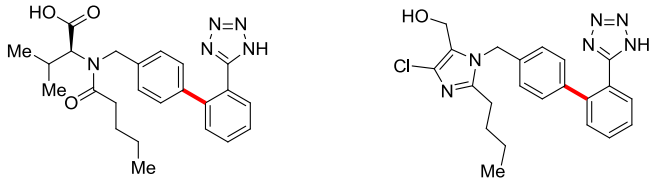

Fig. 1. Angiotensin-II-receptor blockers bearing 5-biaryl tetrazoles.

5-Biaryl-substituted tetrazoles are the common structural motifs of numerous nonpeptidic ARBs. Thus far, the biaryl moieties were mostly constructed through conventional palladium-catalyzed cross-coupling reactions between electrophilic aryl halides and nucleophilic organometallic or main group element reagents.[2] Unfortunately, the prerequisite nucleophiles are not readily available and their syntheses involve a number of reaction steps, which generate undesired waste. A significantly more atom- and step-economical approach is represented by the direct arylation of otherwise unreactive C–H bonds.[3,4] Particularly, ruthenium(II) complexes have in recent years attracted significant research interest because of their cost-effective nature as well as their excellent chemoselectivity and versatility.[5] In this context, Seki very recently reported on a ruthenium-catalyzed direct arylation approach to ABRs utilizing PPh_3[6,7] as the ligand—yet with NMP as the solvent, which was recently[8] shown to contain impurities that significantly influence the reproducibility of the ruthenium catalyst.[9]

In 2008, we have introduced carboxylates as cocatalytic additives for very robust and reliable ruthenium(II)-catalyzed C–H bond functionalizations.[10] Subsequently, preformed or in situ generated ruthenium(II) biscarboxylates were applied for various C–H bond activation reactions, and were thereby identified as arguably the most broadly applicable tools for ruthenium-catalyst direct arylations[11,12] and alkylations.[11g,13] In consideration of the particular importance of 5-biaryl-substituted tetrazoles in medicinal chemistry, we naturally became attracted by probing our ruthenium(II) biscarboxylates as the catalysts for direct C–H bond arylations of 5-aryl tetrazoles. Hence, in contrast to phosphine ligands, we found carboxylates to display a significant rate-acceleration in the ruthenium(II)-catalyzed synthesis of 5-biaryl-substituted tetrazoles,[14] which, inter alia, enabled direct arylations to be performed in apolar solvents and at low catalyst loadings.

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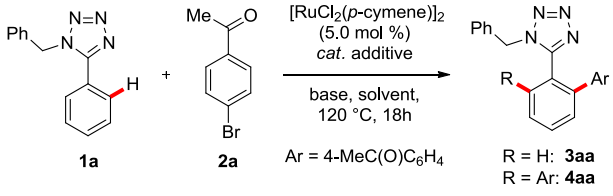
2. Results and discussion

2.1. Optimization studies

At the outset of our studies, we tested various reaction conditions for the desired ruthenium(II)-catalyzed direct arylation of 5-aryl 1*H*-tetrazole **1a** with aryl bromide **2a** (Table 1). With toluene as the solvent, the previously reported ruthenium catalyst[9] derived from phosphine PPh_3 only provided an unsatisfactory low yield of biaryl **3aa** (entry 1),[15] which proved to be comparable to the one obtained in the absence of any cocatalytic additive (entry 2). On the contrary, significantly improved yields of desired product **3aa** were realized when employing carboxylates as the cocatalytic additives (entries 3–7). Not surprisingly, the direct arylation did not occur in the absence of the ruthenium catalyst (entry 8). Likewise, reactions with H_2O as the reaction medium turned out to be unsuccessful (entry 9), while other organic solvents, including 1,4-dioxane, NMP or DMA, were viable alternatives (entries 10–12). C–H bond functionalizations in the absence of the stoichiometric base failed to yield the desired product **3aa** (entry 13). Likewise, carbonate bases other than K_2CO_3 were found to be considerably less effective (entries 14 and 15). Interestingly, the use of KO_2CMes as the stoichiometric base completely inhibited the catalytic reaction (entry 16). As to further applications it is, however, noteworthy that inexpensive KOAc proved to be a suitable stoichiometric base for efficient direct arylations, notably even in the absence of a cocatalytic additive (entries 17–19). Finally, the complex $[RuBr_2(p\text{-cymene})]_2$ was found to be less effective as compared to its chloro analogue (entry 20).

Table 1
Optimization of the direct arylation with arene **1a**[a]

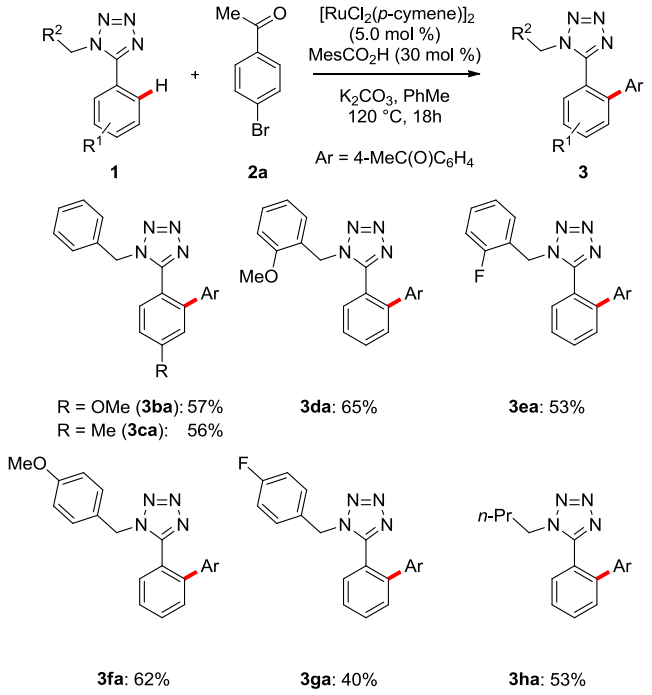


Entry	Additive	Base	Solvent	**3aa** (%)	**4aa** (%)
1	PPh_3	K_2CO_3	PhMe	47	—
2	—	K_2CO_3	PhMe	34	2
3	KOAc	K_2CO_3	PhMe	52	8
4	*t*-$BuCO_2H$	K_2CO_3	PhMe	60	10
5	1-$AdCO_2H$	K_2CO_3	PhMe	61	9
6	KO_2CMes	K_2CO_3	PhMe	64	8
7	*$MesCO_2H$*	*K_2CO_3*	*PhMe*	*64*	*9*
8	$MesCO_2H$[b]	K_2CO_3	PhMe	—	—
9	$MesCO_2H$	K_2CO_3	H_2O	—	—
10	$MesCO_2H$	K_2CO_3	1,4-Dioxane[c]	45	12
11	$MesCO_2H$	K_2CO_3	NMP[d]	46	15
12	$MesCO_2H$	K_2CO_3	DMA	50	19
13	KO_2CMes	—	PhMe	—	—
14	$MesCO_2H$	Na_2CO_3	PhMe	31	—
15	$MesCO_2H$	Cs_2CO_3	PhMe	41	8
16	—	KO_2CMes	PhMe	—	—
17	—	KOAc	PhMe	70	2
18	$MesCO_2H$	KOAc	PhMe	—	—
19	KPF_6	KOAc	PhMe	46	—
20	$MesCO_2H$[e]	K_2CO_3	PhMe	58	7

[a] General reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (10–30 mol %), K_2CO_3 (1.00 mmol), PhMe (2.0 mL), 120 °C, 18 h; yields of isolated products.
[b] Without $[RuCl_2(p\text{-cymene})]_2$.
[c] 100 °C.
[d] 140 °C.
[e] $[RuBr_2(p\text{-cymene})]_2$ (5.0 mol %).

2.2. Scope and limitations

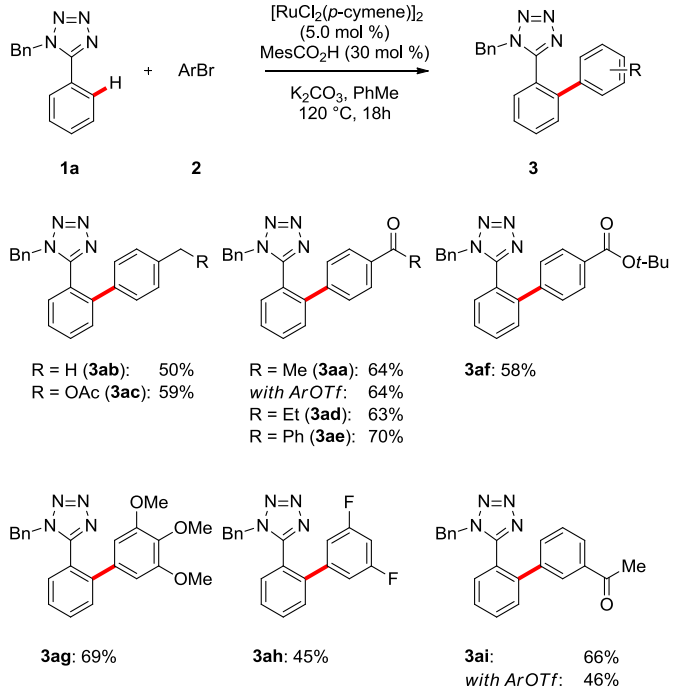
Thereafter, we tested the scope of carboxylate-assisted ruthenium(II)-catalyzed direct arylations with $MesCO_2H$ as the cocatalytic additive and K_2CO_3 as the base (Scheme 1), since this system gave the highest overall yield of mono- and diarylated products, and because it had previously proven to be very robust and most generally applicable. Initially, we set out to unravel the effect of the *N*-substituent of the tetrazole directing group in substrates **1b**–**1h**. Interestingly, the tetrazole-substituted arene **1d** displaying an electron-donating *ortho*-substituent on the benzyl moiety gave a higher yield of the desired product as compared to the fluoro-substituted derivative **1e**. A comparable observation was made with *para*-benzyl-substituted starting materials **1f** and **1g**. On the contrary, an *N*-alkyl-substituted substrate **1h** underwent the catalytic C–H bond functionalization with a lower efficacy.



Scheme 1. Scope of carboxylate-assisted direct arylations of arenes **1**.

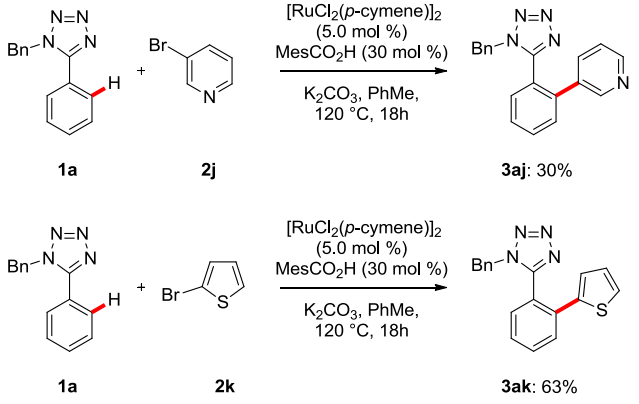
Given that the simple *N*-benzyl-substituted tetrazole derivative **1a** provided satisfactory results, we subsequently utilized starting material **1a** for exploring the scope with respect to the electrophilic aryl bromides **2** (Scheme 2). Importantly, our optimized catalytic system was found to be broadly applicable and displayed a synthetically useful chemoselectivity. Hence, valuable electrophilic functional groups, including enolizable ketones, or esters, were well tolerated to furnish the desired products **3aa**–**3af** in high yields. Interestingly, the electron-rich substrate **2g** was more efficiently converted than was the 3,5-difluoro-substituted derivative **2h**. This reactivity pattern is in agreement with previous findings in our laboratories,[16–18] and is indicative of a rate-determining reductive elimination (vide infra). Generally, substituents in the *para*- and *meta*-positions of the aryl bromides **2** were well tolerated, while less satisfactory results were obtained with *ortho*-substituted electrophiles. Moreover, the catalytic system was not restricted to aryl bromides **2**, but phenol-derived aryl triflates were also found to be suitable arylating reagents, as illustrated for the synthesis of products **3aa** and **3ai**.

Given the importance of heteroarenes in medicinal chemistry,[19] we were particularly pleased to find that heteroaryl bromides **2j**



Scheme 2. Carboxylate-assisted direct arylations with aryl bromides **2**.

and **2k** were also suitable electrophilic substrates (Scheme 3). Again, the more electron-rich electrophile **2k** provided superior results.

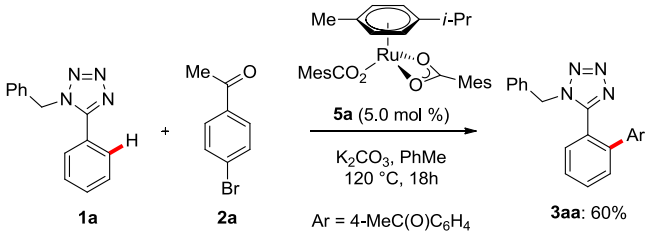


Scheme 3. Direct C–H functionalization with heteroaryl bromides **2**.

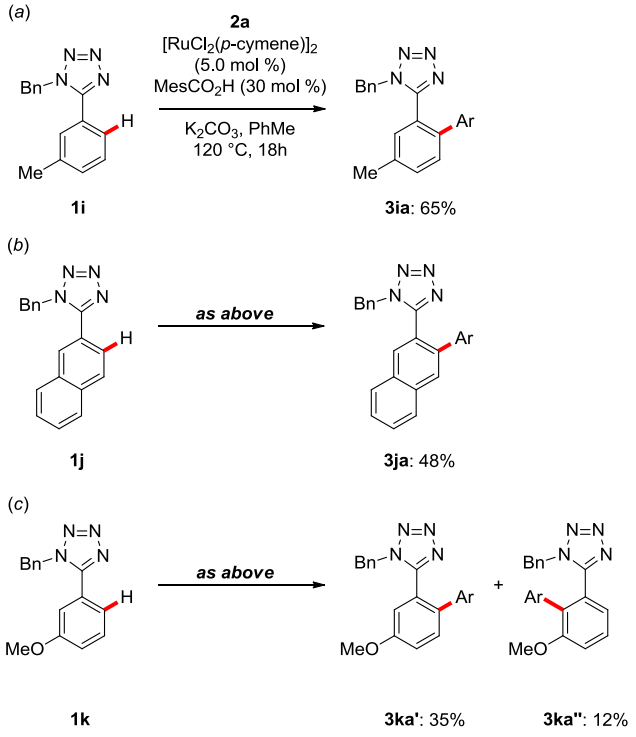
2.3. Mechanistic studies

In consideration of the unique efficiency of our carboxylate-assisted ruthenium(II)-catalyzed direct arylations, we performed mechanistic studies to rationalize the catalysts mode of action. To this end, we tested the performance of the well-defined ruthenium(II) biscarboxylate complex **5a**[11f,n,13] in the direct arylation of arene **1a** (Scheme 4). Notably, the isolated complex **5a** displayed a catalytic activity being comparable to the one observed when using the in situ formed catalytic system (vide supra).

Intramolecular competition experiments with *meta*-substituted substrates **1i** and **1j** showed that steric interactions were largely governing the site-selectivity of the C–H bond functionalization process (Scheme 5a, and b). However, substrate **1k** bearing a heteroatom-substituent in the *meta*-position delivered significant amounts of the product **3ka″** via direct arylation at the more congested C–H bond (Scheme 5c)—a feature that can be rationalized in terms of a secondary directing group effect.

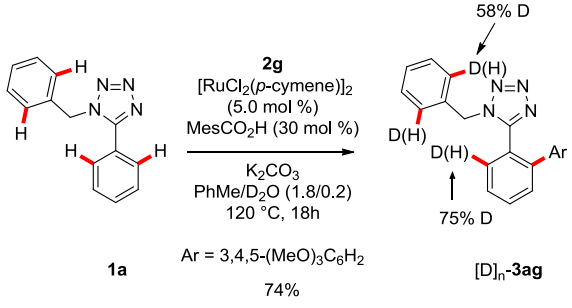


Scheme 4. Direct arylation with ruthenium biscarboxylate **5a**.



Scheme 5. Intramolecular competition experiments (Ar=4-MeC(O)C_6H_4).

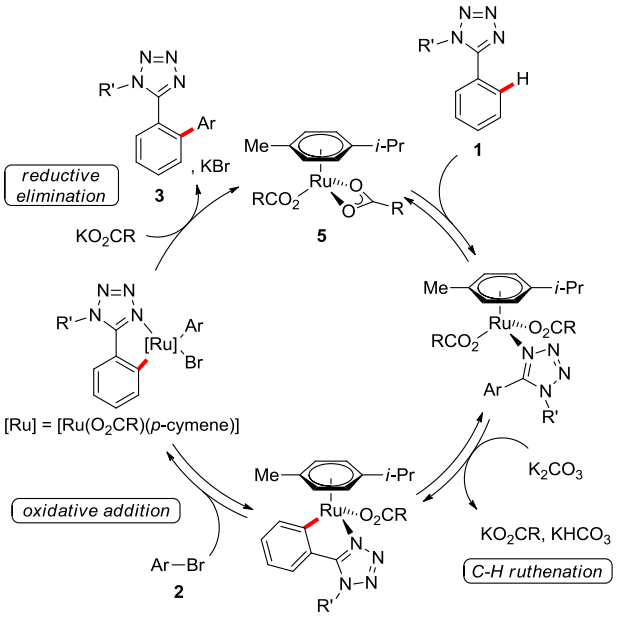
Furthermore, a direct arylation with D_2O as the co-solvent clearly revealed the key *ortho*-C–H bond metalation on the arene to be reversible in nature (Scheme 6). Interestingly, the additional H/D exchange in the *ortho*-position of the *N*-benzyl substituent highlights the potential for C–H bond activation on benzyl-substituted tetrazoles. Furthermore, these findings illustrate direct arylations via six-membered[17] ruthenacycles to be significantly more challenging than transformations through the corresponding five-membered intermediates.



Scheme 6. Direct arylation of arene **1a** in the presence of D_2O.

Based on our mechanistic studies we propose the catalytic cycle to involve initial reversible cyclometalation through chelation-assistance (Scheme 7). Thereafter, formal oxidative addition of

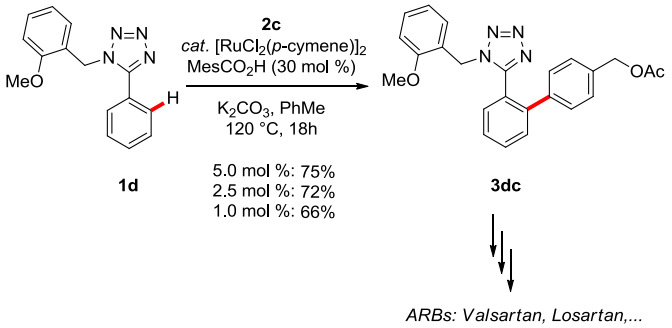
the aryl bromide **2**, followed by rate-limiting reductive elimination furnish the desired product **3**, and thereby regenerate the catalytically active ruthenium(II) complex **4a**.



Scheme 7. Proposed catalytic cycle.

2.4. Synthesis of the key ARB intermediate

Given the significant interest in atom- and step-economical syntheses of antihypertensive ARBs, we became attracted by further testing the direct arylation of arene **1d** with *para*-substituted aryl bromide **2c** (Scheme 8). Notably, the carboxylate-assisted ruthenium-catalyzed C–H bond functionalization occurred very efficiently—even with significantly reduced catalyst loadings.



Scheme 8. Preparation of the key ARB precursor **3dc**.

3. Conclusions

In summary, we have disclosed the significant rate-acceleration exerted by carboxylates in ruthenium(II)-catalyzed direct arylations of arenes bearing tetrazoles as the site-selectivity ensuring directing groups. Thus, in situ generated as well as well-defined ruthenium(II) biscarboxylate complexes enabled highly efficient direct arylations of 5-aryl tetrazoles with excellent chemo- and site-selectivity as well as ample scope. The optimized catalytic system was utilized for the preparation of the key angiotensin-II-receptor blocker intermediate with low catalyst loadings. Mechanistic studies were indicative of a reversible C–H bond metalation and a rate-limiting reductive elimination.

4. Experimental

4.1. General

All catalytic reactions were carried out on a 0.5–1.0 mmol scale under N_2 using pre-dried glassware. Chemicals were obtained from commercial sources and were used without further purification. The tetrazoles **1** were prepared according to a literature procedure.[9b] Toluene was distilled over sodium/benzophenone or was purified using an M. Braun SPS-800 solvent purification system. Yields refer to isolated compounds, estimated to be >95% pure by ^{1}H NMR. Chromatography: Merck silica gel 60 (230–400 mesh). NMR: spectra were recorded on a Varian Unity 300, Varian Mercury 300, or a Varian Inova 500 in the solvent indicated; chemical shifts (δ) are given in parts per million (ppm), coupling constants (J) in hertz (Hz).

4.2. Representative procedure for ruthenium-catalyzed direct arylations of tetrazoles: 1-{2′-(1-benzyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl}ethanone (3aa)and 1,1′-{2′-(1-benzyl-1*H*-tetrazol-5-yl)-[1,1′:3′,1″-terphenyl]-4,4″-diyl}diethanone (4aa)

A suspension of **1a** (120 mg, 0.51 mmol), **2a** (112 mg, 0.56 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (27.6 mg, 0.17 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.1 mg, 0.026 mmol, 5.2 mol %) in dry PhMe (2.0 mL) was stirred for 18 h at 120 °C. Then, H_2O (50 mL) was added at ambient temperature. The aqueous layer was extracted with CH_2Cl_2 (35×0 mL), the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) to yield **3aa** (116 mg, 64%) as white solids and **4aa** (21 mg, 9%) as a white solid. Compound **3aa**. Mp: 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.87–7.78 (m, 2H), 7.67 (td, J=7.7, 1.4 Hz, 1H), 7.57 (dd, J=7.7, 1.4 Hz, 1H), 7.49 (td, J=7.7, 1.4 Hz, 1H), 7.37 (dd, J=7.7, 1.4 Hz, 1H), 7.24–7.09 (m, 5H), 6.85–6.69 (m, 2H), 4.88 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.4 (C_q), 154.2 (C_q), 143.3 (C_q), 140.7 (C_q), 136.3 (C_q), 132.8 (C_q), 131.7 (CH), 131.2 (CH), 130.3 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 122.7 (C_q), 51.0 (CH_2), 26.6 (CH_3). IR (ATR): 1680, 1496, 1437, 1402, 1357, 1265, 959, 849, 721, 700 cm^{-1}. MS (EI) m/z (relative intensity): 354 (12), 353 (35), 325 (10), 206 (8), 192 (8), 179 (8), 164 (11), 151 (6), 91 (100), 65 (15), 43 (38). HRMS (EI) m/z calcd for $C_{22}H_{18}N_4O^+$ [M^+] 354.1481, found 354.1468.

Compound **4aa**. Mp: 220–223 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83–7.64 (m, 5H), 7.54 (d, J=7.7 Hz, 2H), 7.24 (ddt, J=7.8, 7.4, 1.4 Hz, 1H), 7.14 (t, J=7.4 Hz, 2H), 7.07–6.96 (m, 4H), 6.69 (dd, 7.1, 1.6 Hz, 2H), 4.72 (s, 2H), 2.55 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.4 (C_q), 152.3 (C_q), 143.2 (C_q), 142.5 (C_q), 136.2 (C_q), 132.3 (C_q), 131.5 (C_q), 129.9 (CH), 129.2 (CH), 128.9 (CH), 128.3 (CH), 128.1 (CH), 121.2 (C_q), 50.9 (CH_2), 26.6 (CH_3). IR (ATR): 1683, 1604, 1424, 1394, 1354, 1264, 1111, 962, 825, 803, 726, 702, 596 cm^{-1}. MS (EI) m/z (relative intensity): 473 (12), 472 (37), 471 (35), 283 (12), 239 (19), 91 (100), 65 (10), 43 (74). HRMS (EI) m/z calcd for $C_{30}H_{24}N_4O_2^+$ [M^+] 472.1899, found 472.1902.

4.3. 1-[2′-(1-Benzyl-1*H*-tetrazol-5-yl)-5′-methoxy-(1,1′-biphenyl)-4-yl]ethanone (3ba)

Following the general procedure, **1b** (136 mg, 0.51 mmol), **2a** (109 mg, 0.60 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ba** (108 mg, 57%) was obtained as a green solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1). Mp: 153–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.80

(d, J=8.3 Hz, 2H), 7.29 (d, J=8.5 Hz, 1H), 7.24–7.09 (m, 5H), 7.05 (d, J=2.6 Hz, 1H), 6.99 (dd, J=8.5, 2.6 Hz, 1H), 6.79 (d, 2H), 4.87 (s, 2H), 3.90 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=197.3 (C_q), 161.8 (C_q), 154.1 (C_q), 143.3 (C_q), 142.2 (C_q), 136.2 (C_q), 132.9 (C_q), 132.6 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 115.9 (CH), 114.4 (C_q), 113.8 (CH), 55.6 (CH_3), 50.7 (CH_2), 26.6 (CH_3). IR (ATR): 1677, 1601, 1467, 1444, 1268, 1221, 848 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{20}N_4O_2$ [M+H$^+$] 385.1659, found 385.1658.

4.4. 1-[2′-(1-Benzyl-1*H*-tetrazol-5-yl)-5′-methyl-(1,1′-biphenyl)-4-yl]ethanone (3ca)

Following the general procedure, **1c** (127 mg, 0.50 mmol), **2a** (109 mg, 0.55 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and [$RuCl_2$(p-cymene)]$_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ca** (104 mg, 56%) was obtained as a white solid after purification by column chromatography on silica gel (n-hexane/EtOAc 5:1). Mp: 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.82 (d, J=8.6 Hz, 2H), 7.36 (dt, J=1.5, 0.8, 0.8 Hz, 1H), 7.32–7.06 (m, 7H), 6.80–6.74 (m, 2H), 4.85 (s, 2H), 2.56 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=197.4 (C_q), 154.3 (C_q), 143.6 (C_q), 142.0 (C_q), 140.6 (C_q), 136.2 (C_q), 132.9 (C_q), 131.1 (CH), 130.1 (CH), 129.3 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 119.7 (C_q), 50.8 (CH_2), 26.6 (CH_3), 21.5 (CH_3). IR (ATR): 1675, 1601, 1495, 1453, 1268, 1229, 833 cm^{-1}. HRMS (ESI) m/z calcd for $C_{23}H_{20}N_4O$ [M+H$^+$] 369.1710; found 369.1708.

4.5. 1-(2′-(1-(2-Methoxybenzyl)-1*H*-tetrazol-5-yl))-([1,1′-biphenyl]-4-yl)ethanone (3da)

Following the general procedure, **1d** (268 mg, 1.00 mmol), **2a** (217 mg, 1.10 mmol), K_2CO_3 (278 mg, 2.00 mmol), $MesCO_2H$ (53.1 mg, 0.32 mmol, 32 mol %), and [$RuCl_2$(p-cymene)]$_2$ (31.4 mg, 0.05 mmol, 5.0 mol %) were stirred in PhMe (3.0 mL) for 18 h at 120 °C. Compound **3da** (250 mg, 65%) was obtained as a light yellow solid after purification by column chromatography on silica gel (n-hexane/EtOAc 4:1→2:1). Mp: 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.89–7.77 (m, 2H), 7.66 (ddd, J=7.8, 7.1, 1.6 Hz, 1H), 7.57 (ddd, J=7.7, 1.4, 0.6 Hz, 1H), 7.51 (td, J=7.4, 1.4 Hz, 1H), 7.45 (ddd, J=7.8, 1.6, 0.6 Hz, 1H), 7.24–7.15 (m, 3H), 6.80 (dd, J=7.5, 2.0 Hz, 1H), 6.74 (td, J=7.4, 1.0 Hz, 1H), 6.69 (dd, J=8.4, 1.0 Hz, 1H), 4.80 (s, 2H), 3.51 (s, 3H), 2.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=197.4 (C_q), 156.6 (C_q), 154.3 (C_q), 143.6 (C_q), 140.8 (C_q), 136.1 (C_q), 131.3 (CH), 131.3 (CH), 130.1 (CH), 130.1 (CH), 129.8 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 123.2 (C_q), 121.2 (C_q), 120.5 (CH), 110.3 (CH), 55.0 (CH_3), 46.0 (CH_2), 26.6 (CH_3). IR (ATR): 1686, 1603, 1495, 1402, 1251, 1018, 844, 772, 760, 599 cm^{-1}. MS (EI) m/z (relative intensity): 384 (24), 383 (25), 356 (8), 235 (10), 207 (32), 206 (35), 179 (15), 164 (15), 121 (100), 91 (70). HRMS (EI) m/z calcd for $C_{23}H_{19}N_4O_2^+$ [M−H$^+$] 383.1508, found 383.1510.

4.6. 1-(2′-(1-(2-Fluorobenzyl)-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)ethanone (3ea)

Following the general procedure, **1e** (130 mg, 0.51 mmol), **2a** (109 mg, 0.55 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and [$RuCl_2$(p-cymene)]$_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ea** (100 mg, 53%) was obtained as a colorless solid after purification by column chromatography on silica gel (n-hexane/EtOAc 5:1). Mp: 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.88–7.80 (m, 2H), 7.68 (ddd, J=8.0, 7.0, 1.0 Hz, 1H), 7.58 (ddd, J=8.0, 1.0, 1.0 Hz, 1H), 7.51 (td, J=7.0, 1.0 Hz, 1H), 7.42 (dd, J=8.0, 1.0 Hz, 1H), 7.25–7.19 (m, 3H), 6.99–6.85 (m, 2H), 6.80 (td, J=7.0, 2.0 Hz, 1H), 4.87 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=197.3 (C_q), 160.0 (C_q, J_{C-F}=249 Hz), 154.4 (C_q), 143.3 (C_q), 140.7 (C_q), 136.3 (C_q), 131.7 (CH), 131.2 (CH), 130.7 (CH, J_{C-F}=8Hz), 130.2 (CH), 129.8 (CH, J_{C-F}=3 Hz), 128.9 (CH), 128.8 (CH), 128.5(CH), 124.4 (CH, J_{C-F}=4 Hz), 122.5 (C_q), 120.2 (C_q, J_{C-F}=14 Hz), 115.5 (CH, J_{C-F}=21 Hz), 44.4 (CH_2, J_{C-F}=5 Hz), 26.6 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ=−(117.9–118.0) (m). IR (ATR): 1680, 1602, 1493, 1468, 1450, 1264, 1240, 799, 766 cm^{-1}. HRMS (ESI) m/z calcd for $C_{22}H_{17}N_4OF$ [M+H$^+$] 373.1459, found 373.1454.

4.7. 1-(2′-(1-(4-Methoxybenzyl)-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)ethanone (3fa)

Following the general procedure, **1f** (136 mg, 0.51 mmol), **2a** (109 mg, 0.55 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and [$RuCl_2$(p-cymene)]$_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2 mL) for 18 h at 120 °C. Compound **3fa** (121 mg, 62%) was obtained as a white solid after purification by column chromatography on silica gel (n-hexane/EtOAc 5:1). Mp: 117–119 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.84–7.77 (m, 2H), 7.67 (td, J=7.6, 1.4 Hz, 1H), 7.58 (dd, J=7.8, 1.4 Hz, 1H), 7.50 (td, J=7.5, 1.4 Hz, 1H), 7.36 (dd, J=7.7, 1.4 Hz, 1H), 7.21–7.12 (m, 2H), 6.68–6.61 (m, 4H), 4.81 (s, 2H), 3.72 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=197.4 (C_q), 159.7 (C_q), 153.9 (C_q), 143.3 (C_q), 140.7 (C_q), 136.2 (C_q), 131.6 (CH), 131.2 (CH), 130.2 (CH), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 124.8 (C_q), 122.8 (C_q), 114.0 (CH), 55.2 (CH_3), 50.5 (CH_2), 26.6 (CH_3). IR (ATR): 1677, 1513, 1400, 1326, 1244, 1179, 1100, 1034, 775 cm^{-1}. HRMS (EI) m/z calcd for $C_{23}H_{20}N_4O_2$ [M+H$^+$] 385.1659, found 385.1657.

4.8. 1-(2′-(1-(4-Fluorobenzyl)-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)ethanone (3ga)

Following the general procedure, **1g** (127 mg, 0.50 mmol), **2a** (109 mg, 0.55 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and [$RuCl_2$(p-cymene)]$_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ga** (74 mg, 40%) was obtained as a white solid after purification by column chromatography on silica gel (n-hexane/EtOAc 5:1). Mp: 156–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.88–7.78 (m, 2H), 7.68 (td, J=7.6, 1.4 Hz, 1H), 7.58 (ddd, J=7.8, 1.4, 0.6 Hz, 1H), 7.50 (td, J=7.5, 1.4 Hz, 1H), 7.36 (ddd, J=7.7, 1.4, 0.6 Hz, 1H), 7.24–7.13 (m, 2H), 6.91–6.67 (m, 4H), 4.82 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=197.3 (C_q), 162.6 (C_q, J_{C-F}=249 Hz), 154.1 (C_q), 143.2 (C_q), 140.6 (C_q), 136.3 (C_q), 131.8 (CH), 131.2 (CH), 130.3 (CH), 129.6 (CH, J_{C-F}=8 Hz), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (C_q, J_{C-F}=3 Hz), 122.6 (C_q), 115.8 (CH, J_{C-F}=22 Hz), 50.2 (CH_2), 26.6 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$): δ=−(112.2–112.4) (m). IR (ATR): 1679, 1601, 1469, 1453, 1402, 1263, 1221, 958, 768 cm^{-1}. HRMS (ESI) m/z calcd for $C_{22}H_{17}N_4OF$ [M+H$^+$] 373.1459, found 373.1454.

4.9. 1-{2′-(*n*-Butyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl} ethanone (3ha)

Following the general procedure, **1h** (102 mg, 0.50 mmol), **2a** (111 mg, 0.55 mmol), K_2CO_3 (143 mg, 1.03 mmol), $MesCO_2H$ (26.9 mg, 0.16 mmol, 32 mol %), and [$RuCl_2$(p-cymene)]$_2$ (15.8 mg, 0.026 mmol, 5.2 mol %) were stirred in PhMe (2.0 mL) for 18h at 120 °C. Compound **3ha** (85 mg, 53%) was obtained as a colorless oil after purification by column chromatography on silica gel (n-hexane/EtOAc 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.91–7.84 (m, 2H), 7.74–7.65 (m, 1H), 7.62–7.55 (m, 3H), 7.23 (d, J=7.5 Hz, 2H), 3.55 (dd, J=8.1, 6.8 Hz, 2H), 2.57 (s, 3H), 1.43–1.29 (m, 2H), 1.10–0.91 (m, 2H), 0.69 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.3 (C_q), 154.2 (C_q), 143.5 (C_q), 140.5 (C_q), 136.3 (C_q), 131.7 (CH), 131.5 (CH), 130.3 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 122.9 (C_q), 47.0 (CH_2), 30.6 (CH_2), 26.6 (CH_3), 19.4 (CH_2), 13.1 (CH_3). IR (film): 2960, 1681,

1604, 1438, 1357, 1262, 1005, 841, 763, 596 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 319 (100) [M−H^+], 291 (45), 263 (8), 249 (18), 178 (14), 151 (10), 43 (30). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{19}N_4O^+$ [M−H^+] 319.1559, found 319.1564.

4.10. 1-Benzyl-5-(4′-methyl-[1, 1′-biphenyl]-2-yl)-1*H*-tetrazole (3ab)

Following the general procedure, **1a** (118 mg, 0.50 mmol), **2b** (97 mg, 0.57 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ab** (82 mg, 50%) was obtained as a colorless solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 6:1). Mp: 143–144 °C. ^1H NMR (300 MHz, $CDCl_3$) δ=7.67–7.52 (m, 2H), 7.45–7.30 (m, 2H), 7.23–7.06 (m, 5H), 7.06–7.00 (m, 2H), 6.81–6.64 (m, 2H), 4.77 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=154.7 (C_q), 141.6 (C_q), 138.0 (C_q), 135.9 (C_q), 133.1 (C_q), 131.5 (CH), 131.2 (CH), 130.1 (CH), 129.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.5 (CH), 122.6 (C_q), 50.8 (CH_2), 21.1 (CH_3). IR (ATR): 1597, 1495, 1470, 1457, 1240, 1074, 756 cm^{-1}. HRMS (ESI) *m*/*z* calcd for $C_{21}H_{18}N_4$ [M+H^+] 327.1604; found 327.1604.

4.11. (2′-(1-Benzyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)methyl acetate (3ac)

Following the general procedure, **1a** (119 mg, 0.50 mmol), **2c** (134 mg, 0.58 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (30.2 mg, 0.18 mmol, 36 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.8 mg, 0.027 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ac** (114 mg, 59%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1). Mp: 72–73 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.64 (dddd, *J*=7.8, 7.1, 1.4, 0.7 Hz, 1H), 7.55 (ddd, *J*=7.8, 1.4, 0.7 Hz, 1H), 7.44 (tdd, *J*=7.3, 1.4, 0.7 Hz, 1H), 7.34 (dt, *J*=8.4, 0.7 Hz, 1H), 7.29–7.23 (m, 2H), 7.21–7.09 (m, 5H), 6.78–6.72 (m, 2H), 5.08 (s, 2H), 4.82 (s, 2H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.7 (C_q), 154.5 (C_q), 141.2 (C_q), 138.6 (C_q), 135.9 (C_q), 133.0 (C_q), 131.6 (CH), 131.2 (CH), 130.3 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 122.6 (C_q), 65.5 (CH_2), 50.8 (CH_2), 20.9 (CH_3). IR (ATR): 1724, 1498, 1469, 1248, 1108, 971, 926, 834, 824, 740, 716, 700, 666, 560, 528 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 384 (50) [M], 383 (100), 355 (17), 251 (20), 205 (20), 192 (8), 178 (20), 177 (28), 165 (12), 151 (10), 91 (86), 65 (14), 43 (21). HRMS (EI) *m*/*z* calcd for $C_{23}H_{19}N_4O_2^+$ [M−H^+] 383.1508, found 383.1503.

4.12. 1-(2′-(1-Benzyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl) propan-1-one (3ad)

Following the general procedure, **1a** (122 mg, 0.51 mmol), **2d** (126 mg, 0.58 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25.6 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ad** (119 mg, 63%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1). Mp: 90–91 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.85 (dt, *J*=8.5, 1.5 Hz, 2H), 7.67 (ddd, *J*=8.8, 7.8, 1.2 Hz, 1H), 7.58 (ddd, *J*=7.8, 1.3, 0.5 Hz, 1H), 7.49 (td, *J*=7.5, 1.4 Hz, 1H), 7.37 (ddd, *J*=7.8, 1.3 Hz, 1H), 7.23–7.10 (m, 5H), 6.77 (d, *J*=6.6 Hz, 2H), 4.86 (s, 2H), 2.97 (q, *J*=7.2 Hz, 2H), 1.23 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=200.0 (C_q), 154.2 (C_q), 143.1 (C_q), 140.7 (C_q), 136.1 (C_q), 132.8 (C_q), 131.6 (CH), 131.1 (CH), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.4 (CH), 127.6 (CH), 122.7 (C_q), 50.9 (CH_2), 31.8 (CH_2), 8.0 (CH_3). IR (ATR): 1682, 1400, 1223, 953, 804, 772, 759, 718, 705, 584 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 368 (30) [M], 367 (85), 339 (32), 206 (15), 192 (25), 178 (17), 164 (21), 151 (12), 91 (100), 65 (15). HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}N_4O^+$ [M−H^+] 367.1559, found 367.1557.

4.13. 2′-(1-Benzyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl(phenyl) methanone (3ae)

Following the general procedure, **1a** (119 mg, 0.50 mmol), **2e** (149 mg, 0.57 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.4 mg, 0.026 mmol, 5.2 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. **3ae** (174 mg, 70%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1). Mp: 123–126 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.79–7.65 (m, 5H), 7.66–7.56 (m, 2H), 7.54–7.45 (m, 3H), 7.38 (dd, *J*=7.8, 1.4 Hz, 1H), 7.25–7.12 (m, 5H), 6.80 (dt, *J*=6.5, 1.6 Hz, 2H), 4.93 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=195.8 (C_q), 154.2 (C_q), 142.7 (C_q), 140.8 (C_q), 137.2 (C_q), 136.8 (C_q), 132.8 (C_q), 132.6 (CH), 131.6 (CH), 131.2 (CH), 130.5 (CH), 130.4 (CH), 129.9 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 126.6 (CH), 128.5 (CH), 128.3 (CH), 122.7 (C_q), 51.0 (CH_2). IR (ATR): 1653, 1600, 1446, 1402, 1276, 1098, 923, 794, 767, 697, 664, 633 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 416 (55) [M], 415 (100), 387 (26), 269 (8), 164 (8), 105 (30), 91 (60), 77 (22), 65 (10). HRMS (ESI) *m*/*z* calcd for $C_{27}H_{21}N_4O^+$ [M+H^+] 417.1715, found 417.1710.

4.14. *tert*-Butyl 2′-(1-benzyl-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl-carboxylate (3af)

Following the general procedure, **1a** (120 mg, 0.51 mmol), **2f** (169 mg, 0.65 mmol), K_2CO_3 (140 mg, 1.00 mmol), $MesCO_2H$ (24.6 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.6 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3af** (121 mg, 58%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 6:1) and recrystallization from EtOAc. Mp: 190–192 °C. ^1H NMR (300 MHz, $CDCl_3$): δ=7.88 (dd, *J*=7.1, 3.0 Hz, 2H), 7.66 (td, *J*=7.6, 1.5 Hz, 1H), 7.58 (dd, *J*=7.6, 1.5 Hz, 1H), 7.47 (td, *J*=7.5, 1.5 Hz, 1H), 7.36 (dd, *J*=7.7, 1.3 Hz, 1H), 7.25–7.10 (m, 5H), 6.76 (dt, *J*=6.9, 1.5 Hz, 2H), 4.83 (s, 2H), 1.59 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=165.0 (C_q), 154.3 (C_q), 142.7 (C_q), 140.9 (C_q), 132.9 (C_q), 131.6 (CH), 131.5 (C_q), 131.2 (CH), 130.2 (CH), 129.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.6 (CH), 122.7 (C_q), 81.4 (C_q), 50.9 (CH_2), 28.1 (CH_3). IR (ATR): 1699, 1470, 1457, 1438, 1401, 1363, 1295, 1161, 1121, 1106, 861, 848, 721, 556, 535 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 412 (55), 411 (100), 355 (57), 339 (15), 327 (19), 209 (13), 164 (15), 91 (86), 57 (31). HRMS (ESI) *m*/*z* calcd for $C_{25}H_{25}N_4O_2^+$ [M+H^+] 413.1978, found 413.1972.

4.15. 1-Benzyl-5-(3′,4′,5′-trimethoxy-[1,1′-biphenyl]-2-yl)-1*H*-tetrazole (3ag)

Following the general procedure, **1a** (118 mg, 0.50 mmol), **2g** (136 mg, 0.60 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ag** (140 mg, 69%) was obtained as a colorless liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1). ^1H NMR (300 MHz, $CDCl_3$) δ=7.67–7.57 (m, 2H), 7.42 (ddd, *J*=7.8, 6.1, 2.5 Hz, 1H), 7.36–7.31 (m, 1H), 7.24–7.09 (m, 3H), 6.81–6.72 (m, 2H), 6.34 (s, 2H), 4.84 (s, 2H), 3.83 (s, 3H), 3.67 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=154.8 (C_q), 153.3 (C_q), 141.4 (C_q), 137.8 (C_q), 133.1 (C_q), 132.9 (C_q), 131.6 (CH), 131.2 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 122.5 (C_q), 105.7 (CH), 60.9 (CH_3), 56.1 (CH_3), 50.7 (CH_2). IR (film): 1584, 1568, 1508, 1470, 1455, 1240, 1122, 1001, 763. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{22}N_4O_3$ [M+H^+] 403.1765, found 403.1766.

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4.16. 1-Benzyl-5-(3′,5′-difluoro-[1,1′-biphenyl]-2-yl)-1*H*-tetrazole (3ah)

Following the general procedure, **1a** (118 mg, 0.50 mmol), **2h** (110 mg, 0.57 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ah** (78 mg, 45%) was obtained as a colorless liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.64 (td, *J*=7.5, 1.4 Hz, 1H), 7.54–7.40 (m, 2H), 7.33 (dd, *J*=8.0, 1.4 Hz, 1H), 7.27–7.10 (m, 3H), 6.85–6.73 (m, 2H), 6.66 (tt, *J*=8.8, 2.3 Hz, 1H), 6.58–6.40 (m, 2H), 5.04 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ=162.7 (C_q, J_{C-F}=250, 13 Hz), 153.8 (C_q), 141.8(C_q, J_{C-F}=9 Hz), 139.8 (C_q, J_{C-F}=2 Hz), 132.8 (C_q), 131.6 (CH), 130.1 (CH), 130.2 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 122.7 (C_q), 111.71 (CH, J_{C-F}=20, 7 Hz), 103.4 (CH, J_{C-F}=25 Hz), 50.1 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ=–(108.16–108.33) (m). IR (film): 1622, 1593, 1497, 1406, 1099, 987, 860, 689 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 348 ([M$^+$] 38), 347 (48), 319 (32), 201 (48), 91 (100). HRMS (EI) *m*/*z* calcd for $C_{20}H_{14}N_4F_2$ [M–H] 347.1108; found 347.1116.

4.17. 1-[2′-(1-Benzyl-1*H*-tetrazol-5-yl)-(1,1′-biphenyl)-3-yl] ethanone (3ai)

Following the general procedure, **1a** (118 mg, 0.50 mmol), **2i** (109 mg, 0.55 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ai** (117 mg, 66%) was obtained as a colorless liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.85 (d, *J*=7.6 Hz, 1H), 7.76 (s, 1H), 7.66 (dd, *J*=7.5, 1.5 Hz, 1H), 7.59 (d, *J*=7.9 Hz, 1H), 7.48 (td, *J*=7.5, 1.4 Hz, 1H), 7.40–7.05 (m, 6H), 6.76 (d, *J*=6.8 Hz, 2H), 4.87 (s, 2H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=197.4 (C_q), 154.3 (C_q), 140.8 (C_q), 139.1 (C_q), 137.4 (C_q), 133.1 (CH), 132.8 (C_q), 131.9 (CH), 131.1 (CH), 130.3 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 122.6 (C_q), 50.9 (CH_2), 26.6 (CH_3). IR (ATR): 1682, 1405, 1357, 1227, 1100, 758 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 354 ([M$^+$] 28), 353 (41), 326 (21), 325 (68), 91 (100). HRMS (EI) *m*/*z* calcd for $C_{22}H_{18}N_4O$ [M–H$^+$] 353.1402, found 353.1411.

4.18. 3-[2-(1-Benzyl-1*H*-tetrazol-5-yl)phenyl]pyridine (3aj)

Following the general procedure, **1a** (118 mg, 0.50 mmol), **2j** (98 mg, 0.62 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3aj** (46 mg, 30%) was obtained as a green liquid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.49 (d, *J*=4.6 Hz, 1H), 8.39 (s, 1H), 7.67 (t, *J*=7.6 Hz, 1H), 7.59–7.44 (m, 2H), 7.40–7.04 (m, 6H), 6.78 (d, *J*=7.0 Hz, 2H), 4.97 (s, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ=153.7 (C_q), 148.9 (CH), 148.8 (CH), 138.3 (C_q), 135.8 (CH), 134.3 (C_q), 132.6 (C_q), 131.6 (CH), 130.8 (CH), 130.3 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 122.8 (CH), 122.7 (C_q), 50.9 (CH_2). IR (film): 1603, 1404, 1274, 1247, 1026, 791, 761. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{15}N_5$ [M+H$^+$] 314.1400, found 314.1399.

4.19. 1-Benzyl-5-{2-(thiophen-2-yl)phenyl}-1*H*-tetrazole (3ak)

Following the general procedure, **1a** (118 mg, 0.50 mmol), **2k** (99 mg, 0.60 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ak** (101 mg, 63%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 6:1). Mp: 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.65 (dd, *J*=8.0, 1.0 Hz, 1H), 7.59–7.53 (m, 1H), 7.39–7.08 (m, 6H), 6.90 (dd, *J*=5.1, 3.6 Hz, 1H), 6.84–6.76 (m, 2H), 6.59 (dd, *J*=3.6, 1.2 Hz, 1H), 4.90 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=154.2 (C_q), 140.1 (C_q), 134.4 (C_q), 132.9 (C_q), 131.5 (CH), 131.4 (CH), 130.0 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.0 (CH), 126.9 (CH), 122.2 (C_q), 50.9 (CH_2). IR (ATR): 1494, 1470, 1457, 1240, 1159, 1098, 1074, 756 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 318 ([M$^+$] 28), 317 (53), 289 (30), 91 (100). HRMS (EI) *m*/*z* calcd for $C_{18}H_{14}N_4S$ [M–H$^+$] 317.0861; found 317.0872.

4.20. 1-{2′-(1-Benzyl-1*H*-tetrazol-5-yl)-4′-methyl-[1,1′-biphenyl]-4-yl}ethanone (3ia)

Following the general procedure, **1i** (126 mg, 0.50 mmol), **2a** (113 mg, 0.57 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (28.2 mg, 0.17 mmol, 34 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.4 mg, 0.026 mmol, 5.2 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ia** (121 mg, 65%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1). Mp: 126–129 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.79 (ddd, *J*=8.3, 2.0, 1.6 Hz, 2H), 7.44 (s, 1H), 7.44 (s, 1H), 7.18 (tdd, *J*=7.4, 2.0, 1.3 Hz, 1H), 7.16–7.10 (m, 5H), 6.74 (d, *J*=7.2 Hz, 2H), 4.83 (s, 2H), 2.54 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.4 (C_q), 154.4 (C_q), 143.4 (C_q), 138.7 (C_q), 137.7 (C_q), 136.0 (C_q), 132.9 (C_q), 132.4 (CH), 131.7 (CH), 130.1 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 122.4 (C_q), 50.9 (CH_2), 26.6 (CH_3), 20.9 (CH_3). IR (ATR): 2918, 1682, 1603, 1405, 1237, 1205, 1072, 955, 830, 717, 702, 601 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 368 (30), 367 (77), 339 (22), 221 (8), 178 (17), 91 (100), 65 (10), 43 (27). MS (EI) *m*/*z* calcd for $C_{23}H_{19}N_4O^+$ [M–H$^+$] 367.1559, found 367.1560.

4.21. 1-[4-{3′-(1″-Benzyl-1*H*-tetrazol-5-yl)naphthalen-2-yl} phenyl]ethanone (3ja)

Following the general procedure, **1j** (144 mg, 0.50 mmol), **2a** (111 mg, 0.56 mmol), K_2CO_3 (141 mg, 1.02 mmol), $MesCO_2H$ (25.4 mg, 0.15 mmol, 30 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.5 mg, 0.026 mmol, 5.2 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3ja** (96.8 mg, 48%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1). Mp: 175–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.02 (s, 1H), 7.96 (dd, *J*=8.2, 1.3 Hz, 1H), 7.90 (s, 1H), 7.84 (dd, *J*=8.5, 1.9 Hz, 3H), 7.69–7.56 (m, 2H), 7.25 (dd, *J*=8.6, 1.9 Hz, 2H), 7.19–7.03 (m, 3H), 6.76 (dd, *J*=6.8, 1.6 Hz, 2H), 4.92 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=197.2 (C_q), 154.2 (C_q), 143.4 (C_q), 136.8 (C_q), 136.0 (C_q), 134.1 (C_q), 132.8 (C_q), 131.9 (C_q), 131.9 (CH), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.6 (CH), 120.3 (C_q), 51.0 (CH_2), 26.7 (CH_3). IR (ATR): 1675, 1597, 1492, 1430, 1356, 1264, 1118, 1099, 956, 836, 735, 603, 476 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 404 (38), 403 (70), 375 (15), 257 (10), 227 (10), 214 (20), 91 (100), 65 (10), 43 (20). HRMS (EI) *m*/*z* calcd for $C_{26}H_{19}N_4O^+$ [M–H$^+$] 403.1559, found 403.1575.

4.22. 1-(2′-(1-Benzyl-1*H*-tetrazol-5-yl)-4′-methoxy-[1,1′-biphenyl]-4-yl)ethanone (3ka′) and 1-(2′-(1-benzyl-1*H*-tetrazol-5-yl)-6′-methoxy-[1,1′-biphenyl]-4-yl)ethanone (3ka″)

Following the general procedure, **1k** (136 mg, 0.51 mmol), **2a** (114 mg, 0.57 mmol), K_2CO_3 (141 mg, 1.02 mmol), $MesCO_2H$ (25.7 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.8 mg, 0.026 mmol, 5.2 mol %) were stirred in PhMe (2.0 mL) for 18 h at

120 °C. Compounds **3ka′** (67.6 mg, 35%) and **3ka″** (22.8 mg, 12%) were obtained as a yellow solid and a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 5:1→4:1→3:1).

Compound **3ka′**. Mp: 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.81 (dt, *J*=8.1, 2.5 Hz, 2H), 7.49 (d, *J*=8.7 Hz, 1H), 7.22–7.10 (m, 6H), 6.81 (d, *J*=2.7 Hz, 1H), 6.77 (dt, *J*=6.8, 1.5 Hz, 2H), 4.84 (s, 2H), 3.77 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=197.1 (C_q), 159.3 (C_q), 154.1 (C_q), 143.1 (C_q), 135.8 (C_q), 132.8 (C_q), 132.8 (C_q), 131.5 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 123.6 (C_q), 118.0 (CH), 115.7 (CH), 55.6 (CH_3), 51.0 (CH_2), 26.6 (CH_3). IR (ATR): 1669, 1603, 1513, 1401, 1269, 1230, 1029, 850, 823, 731, 721, 706, 646, 599 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 384 (25), 383 (65), 355 (20), 236 (10), 151 (12), 91 (100), 65 (14), 43 (19). MS (EI) *m*/*z* calcd $C_{23}H_{19}N_4O^+$ [M−H$^+$] 383.1508, found 383.1518.

Compound **3ka″**. Mp: 59–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.80 (dt, *J*=8.5, 2.0 Hz, 2H), 7.46 (t, *J*=7.7 Hz, 1H), 7.25–7.17 (m, 4H), 7.15 (dd, *J*=8.5, 1.9 Hz, 2H), 6.95 (dd, *J*=7.7, 0.9 Hz, 1H), 6.86 (dt, *J*=6.4, 1.3 Hz, 2H), 4.96 (s, 2H), 3.83 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=197.5 (C_q), 156.9 (C_q), 153.8 (C_q), 139.3 (C_q), 136.0 (C_q), 133.1 (C_q), 130.5 (CH), 129.9 (C_q), 129.7 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.8 (CH), 124.7 (C_q), 122.7 (CH), 113.8 (CH), 56.0 (CH_3), 50.9 (CH_2), 26.5 (CH_3). IR (ATR): 2931, 1679, 1606, 1498, 1435, 1401, 1260, 1080, 1024, 751, 721, 698, 602 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 384 (30), 383 (60), 355 (15), 237 (11), 194 (13), 165 (8), 151 (8), 91 (100), 65 (13), 43 (15). HRMS (ESI) *m*/*z* calcd for $C_{23}H_{21}N_4O_2^+$ [M+H$^+$] 385.1665, found 385.1659.

4.23. Direct arylation with D_2O as the co-solvent

Following the general procedure, **1a** (121 mg, 0.51 mmol), **2a** (137 mg, 0.55 mmol), K_2CO_3 (139 mg, 1.00 mmol), $MesCO_2H$ (25.1 mg, 0.18 mmol, 36 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (16.5 mg, 0.027 mmol, 5.4 mol %) were stirred in a solvent mixture of PhMe and D_2O (1.8/0.2 mL) for 18 h at 120 °C. $[D]_n$-**3ag** (152 mg, 74%) was obtained as a colorless oil after purification by column chromatography on silica gel (*n*-hexane/EtOAc 3:1). The D-incorporation in $[D]_n$-**3ag** was estimated by ^{1}H NMR spectroscopy.

4.24. 1-((2′-(1-(2-Methoxybenzyl)-1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)oxy))propan-2-one) (3dc)[9b]

Following the general procedure, **1d** (134 mg, 0.50 mmol), **2c** (126 mg, 0.55 mmol), K_2CO_3 (140 mg, 1.01 mmol), $MesCO_2H$ (26.7 mg, 0.16 mmol, 32 mol %), and $[RuCl_2(p\text{-cymene})]_2$ (15.4 mg, 0.025 mmol, 5.0 mol %) were stirred in PhMe (2.0 mL) for 18 h at 120 °C. Compound **3dc** (156 mg, 75%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/EtOAc 4:1). Mp: 119–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.64 (ddd, *J*=8.0, 6.5, 2.1 Hz, 1H), 7.55 (ddd, *J*=7.7, 1.3, 0.7 Hz, 1H), 7.51–7.40 (m, 2H), 7.30–7.24 (m, 2H), 7.20 (ddd, *J*=8.5, 6.9, 2.3 Hz, 1H), 7.13 (d, *J*=7.9 Hz, 2H), 6.83–6.72 (m, 2H), 6.69 (d, *J*=8.3 Hz, 1H), 5.08 (s, 2H), 4.75 (s, 2H), 3.51 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.8 (C_q), 156.7 (C_q), 154.6 (C_q), 141.4 (C_q), 139.0 (C_q), 135.7 (C_q), 131.3 (CH), 131.2 (CH), 130.1 (CH), 130.1 (CH), 130.0 (CH), 128.8 (CH), 128.4 (CH), 127.7 (CH), 123.2 (C_q), 121.5 (C_q), 120.5 (CH), 110.3 (CH), 65.6 (CH_2), 55.0 (CH_3), 46.1 (CH_2), 21.0 (CH_3). IR (ATR): 1733, 1538, 1495, 1278, 1099, 923, 838, 521 cm^{-1}. HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}N_4O_3^+$ [M+H$^+$] 415.1770, found 415.1765.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.006.

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