HETEROCYCLES, Vol. 97, No. 1, 2018, pp. 218 - 231. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 30th October, 2017, Accepted, 20th April, 2018, Published online, 18th May, 2018
DOI: 10.3987/COM-17-S(T)4

PALLADIUM-CATALYZED SELECTIVE FORMATION OF SUBSTITUTED PYRROLES FROM ALKENE-TETHERED CYCLIC OXIME ESTERS

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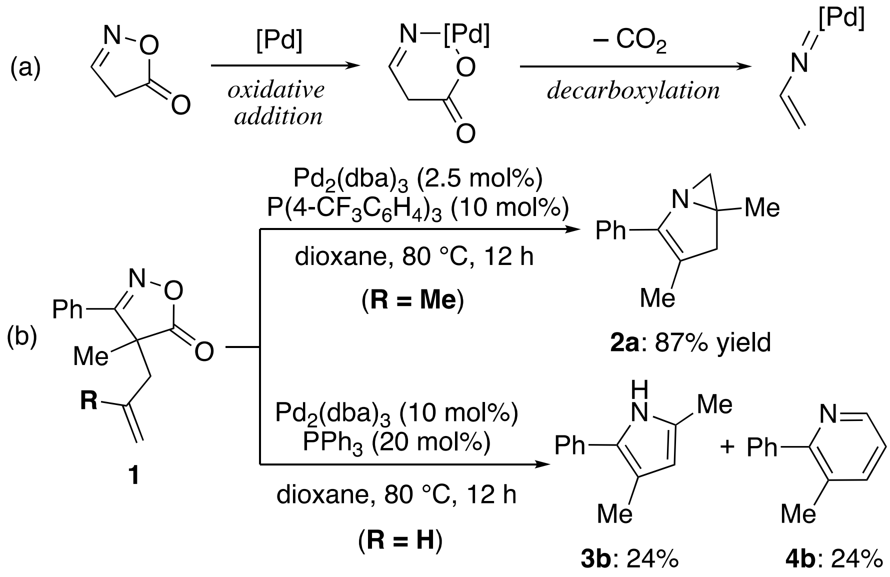
On the occasion of Professor Kiyoshi Tomioka's 70th birthday

Abstract – Isoxazol-5(4*H*)-ones were used as nitrene precursors for the selective formation of trisubstituted pyrroles by applying a palladium-catalyzed decarboxylative ring-reconstruction method. The use of bulky biaryl-type monophosphine ligands was effective for improving the selectivity. Deuterium-labeling experiments suggested a mechanism involving β-hydride elimination followed by reductive elimination from an aza-π-allyl intermediate.

INTRODUCTION

Nitrogen-containing heteroaromatic compounds including pyrroles and pyridines are important structural motifs that are often found in biologically active compounds and functional materials.[1] The development of efficient synthetic methods to access such compounds has been of great interest in synthetic organic chemistry. In recent decades, construction of *N*-heteroaromatics by transition-metal-catalyzed ring-closing reactions have emerged as alternative synthetic approaches.[2]

Our research interest has focused on transition-metal-catalyzed nitrene transfer reactions, which can be used for the direct and efficient construction of C–N bonds.[3-6] We recently reported that cyclic oxime esters (isoxazol-5(4*H*)-ones) underwent N–O bond cleavage[7] followed by decarboxylation in the presence of a palladium catalyst to form vinylnitrene equivalents (Scheme 1a), and that intramolecular aziridination products were selectively obtained by using various alkene-tethered isoxazolones (Scheme 1b).[8a] During these studies,[8] the reaction of isoxazolone **1b**, bearing an allyl group on the 4-position, was performed in the presence of $Pd(dba)_2$ (10 mol%) and PPh_3 (20 mol%) in 1,4-dioxane at 100 °C for 12 h to give the corresponding pyrrole **3b** and pyridine **4b** in 19% and 33% yield, respectively. Herein, we report a palladium-catalyzed decarboxylative intramolecular cyclization of isoxazolones bearing the allyl moiety, forming trisubstituted pyrroles selectively under the optimized conditions.

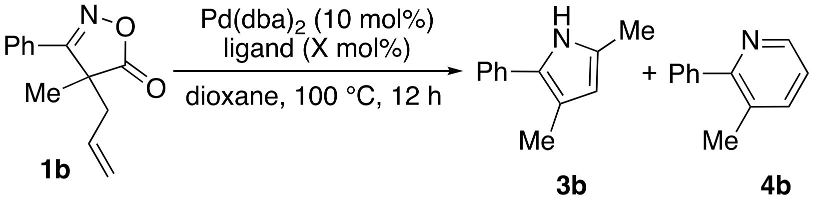


Scheme 1. (a) Generation of imido(nitrene)–palladium complex from isoxazol-5(4*H*)-ones. (b) Palladium-catalyzed decarboxylative cyclization of alkene-tethered isoxazol-5(4*H*)-ones.

RESULTS AND DISCUSSION

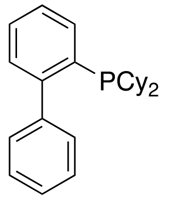
The results of ligand screening studies are summarized in Table 1. Total yields of the two products were in the range of 44–63% in reactions using triarylphosphines with various substituents having differing electronic or steric influence, and the selectivity of the reaction pathway was generally low (entries 2–5). Trialkylphosphines, phosphite, phosphoramide, *N*-heterocyclic carbenes, and arsine were not effective in the selective formation of **3** or **4** (entries 6–14), but the use of PCy_3 resulted in the selective formation of pyridine **4b** (29% isolated yield; entry 7).[9] When bisphosphine ligands with various linkages were used, the total yields were moderate (38–64%) and pyrrole **3b** was formed preferentially (entries 15–24). The selectivity towards **3b** was critically improved when biaryl-di-*t*-butylphosphine ligands were used (entries 26–29). Ligands possessing substituents on the biaryl ring were especially effective (entries 27 and 28). Gratifyingly, pyrrole **3b** was exclusively obtained in 81% isolated yield when the reaction was performed with ligand **L4** (*t*-BuXphos) under slightly modified conditions (entry 29). Notably, the catalytic activity deteriorated significantly in the reaction with ligands **L5** or **L6**, which possess substituents on the aromatic ring directly attached on the phosphine moiety (entries 30 and 31).

Table 1. Palladium-catalyzed reaction of isoxazolone **1b** giving pyrrole **3b** and pyridine **4b**[a]

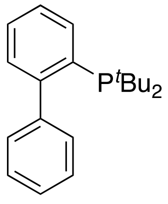


Entry	Ligand	X	conv. of **1b** (%)[b]	**3b** (Yield /%)[b]	**4b** (Yield /%)[b]
1	PPh_3	20	100	19	33
2	$P(4\text{-}MeOC_6H_4)_3$	20	100	31	32
3	$P(4\text{-}CF_3C_6H_4)_3$	20	100	24	24
4	$P(2\text{-}MeC_6H_4)_3$	20	100	30	17
5	P(2-furyl)$_3$	20	100	30	14
6	PBu_3	20	100	14	14
7	PCy_3	20	100	8	33 (29)[c]
8	P^tBu_3	20	52	17	8
9	$P(NMe_2)_3$	20	100	8	31
10	$P(OPh)_3$	20	60	13	3
11	IPr	10	88	25	15
12	IMes	10	100	18	17
13	SIPr	10	100	28	14
14	$AsPh_3$	20	100	27	14
15	dppm	10	100	32	6
16	dppe	10	100	28	15
17	dppp	10	100	38	19
18	dppb	10	100	32	19
19	dpppent	10	100	29	17
20	dpphex	10	100	24	19
21	dppbenz	10	100	39	20
22	dppf	10	100	34	27
23	DPEphos	10	100	45	19
24	xantphos	10	100	27	27
25	**L1**	10	100	27	19
26	**L2**	10	100	50	7
27	**L3**	10	100	61	3
28	**L4**	10	100	69 (59)[c]	0
29[d,e]	**L4**	10	100	90 (81)[c]	0
30	**L5**	10	75	22	0
31	**L6**	10	47	14	1

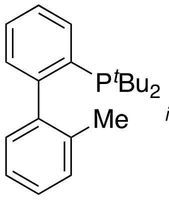
[a] The reactions were carried out with isoxazolone **1b** (0.20 mmol), Pd(dba)$_2$ (10 mol%) and ligand (X mol%) in 1,4-dioxane (1.5 mL). [b] Determined by ^{1}H NMR spectroscopic analysis using nitromethane as internal standard. [c] Isolated yield. [d] The reaction was performed at 80 °C. [e] 2.5 mol% Pd$_2$(dba)$_3$ was used instead of 10 mol% Pd(dba)$_2$.



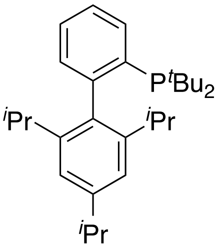
L1



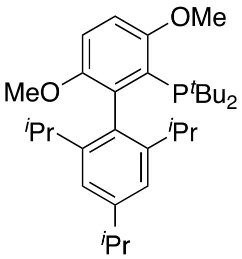
L2



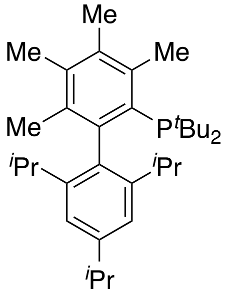
L3



L4



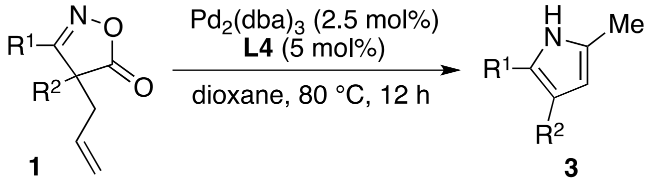
L5



L6

Under the optimized reaction conditions, the decarboxylative cyclization reaction of a variety of alkene-tethered isoxazolones with 5–10 mol% palladium catalyst ($Pd_2(dba)_3$/*t*-BuXphos) gave the corresponding substituted pyrroles selectively (Table 2). Isoxazolones bearing a 2-naphthyl or (4-trifluoromethyl)phenyl group instead of phenyl group also reacted efficiently to give the pyrroles in high yields (entries 2 and 3). However, the yield became slightly lower when the electron-donating methoxy group was substituted on the aromatic ring (entry 4). Isoxazolone **1f**, having two phenyl groups, and isoxazolones **1g** and **1h**, having two allyl groups, also underwent the present reaction to give the pyrroles in high yields (entries 5–7). In all cases, pyridines **4** were observed in less than 5% yield.

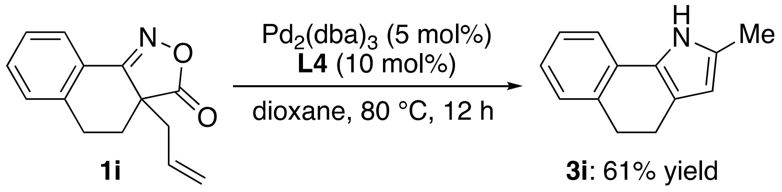
Table 2. Palladium-catalyzed decarboxylative cyclization of isoxazol-5(4*H*)-one **1** giving pyrrole **3**[a]



Entry	Isoxazolone	R^1	R^2	**3** (Yield/%)[b]
1	**1b**	Ph	Me	81
2[c]	**1c**	2-naphthyl	Me	74
3	**1d**	$4\text{-}CF_3C_6H_4$	Me	79
4	**1e**	$4\text{-}MeOC_6H_4$	Me	58
5	**1f**	Ph	Ph	80
6	**1g**	Ph	allyl	76
7	**1h**	Pr	allyl	68

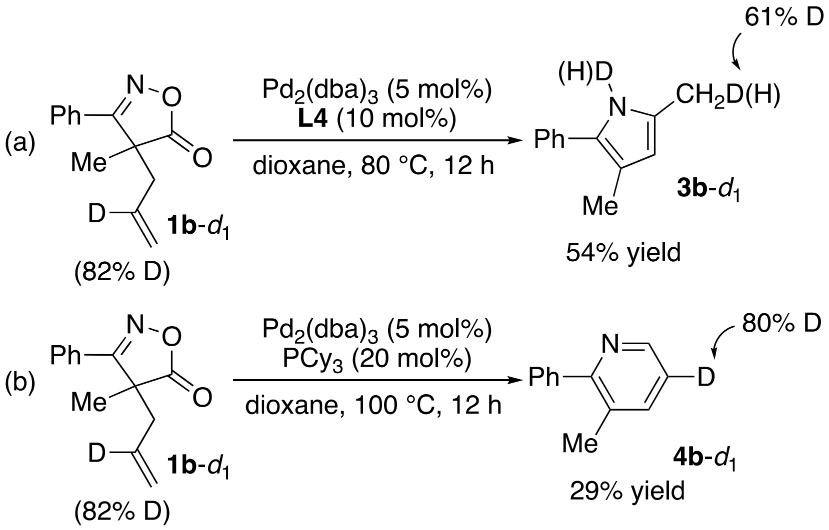
[a] The reactions were carried out with isoxazolone **1** (0.20 mmol), $Pd_2(dba)_3$ (2.5 mol%), and **L4** (5 mol%) in 1,4-dioxane (1.5 mL). [b] Isolated yield. [c] $Pd_2(dba)_3$ (5 mol%) and **L4** (10 mol%) were used.

The polycyclic heteroaromatic rings are generally expected to possess higher functionality than monocyclic systems, because of the expansion of the π-conjugation. In the present catalytic system, tricyclic isoxazolone **1i** was readily converted into compound **3i**, bearing the dihydrobenzoindole framework, in 61% yield (Scheme 2).



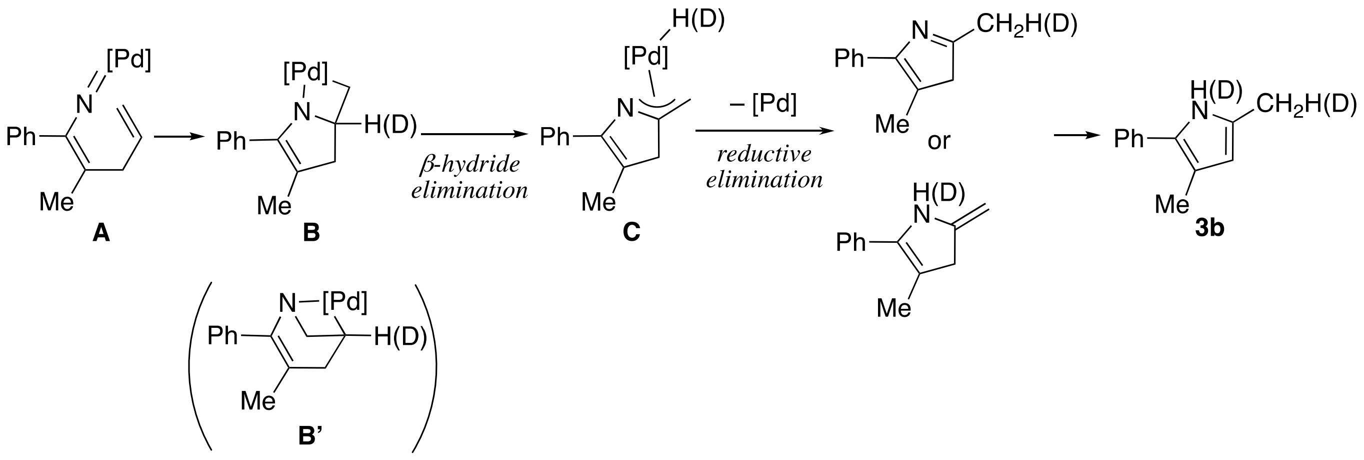
Scheme 2. Formation of tricyclic pyrrole **3i**.

To gain further insights into the reaction mechanism, deuterium-labeling experiments were performed using isoxazolone **1b**-*d*1 (82% D). The corresponding pyrrole **3b**-*d*1 was obtained in 54% yield, with the deuterium incorporation ratio decreased (61% D; Scheme 3a).[10] In contrast, when the reaction of **1b**-*d*1 was performed under conditions in which pyridine **4b** was obtained selectively, **4b**-*d*1 was obtained in almost the same yield as **4b**, with retention of the deuterium incorporation ratio compared to **1b**-*d*1 (29% isolated; 80% D; Scheme 3b). The constant deuterium incorporation ratio measured before and after the reaction indicates that the formation of pyridine **4b**-*d*1 does not include a C–D bond-cleavage process.[11]



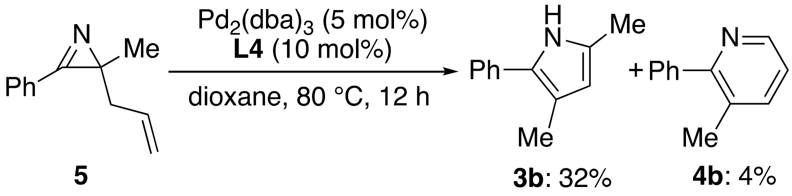
Scheme 3. Deuterium-labeling experiments

Based on these results and on those in the previous report,[7a] nitrene(imido) complex **A** is proposed to be formed as an intermediate (Scheme 4). Intermediate **A** would then undergo cyclization with the internal olefin to form azapalladacycle **B**, which is followed by β-hydride elimination forming aza-π-allyl intermediate **C**.[12] Subsequent reductive elimination forms a C–H(D) bond and affords a 3*H*-pyrrole that can readily isomerize into 1*H*-pyrrole **3** as a final product. The slight decrease in the deuterium incorporation ratio might be attributed to the competing N–H(D) reductive elimination. The bulky coordination sphere of ligand **L4** might assist the selective formation of pyrrole **3** rather than regioisomeric intermediate **B'**.



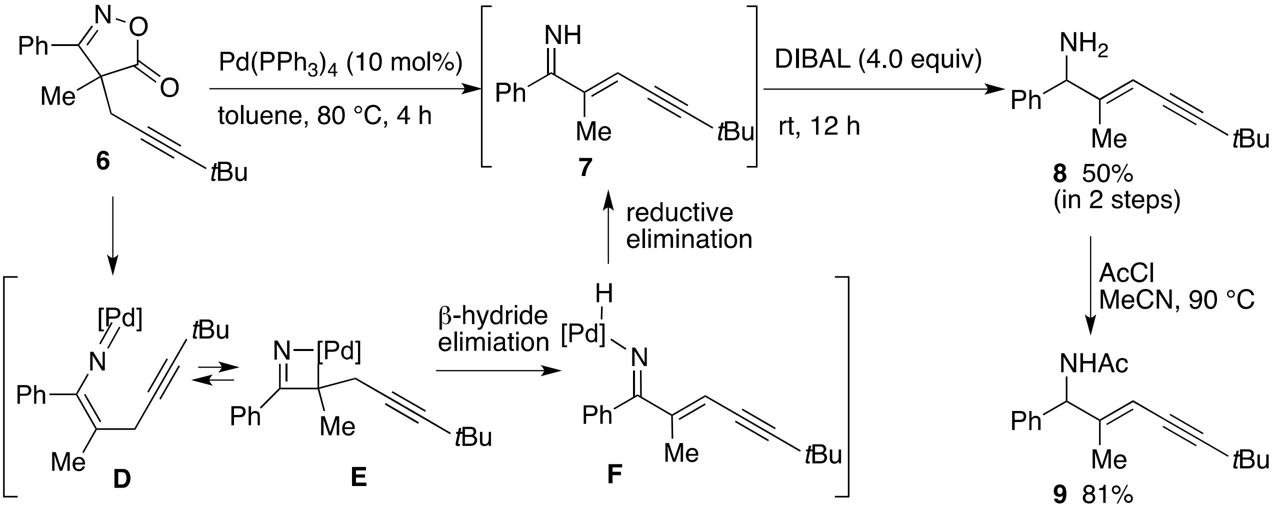
Scheme 4. Proposed mechanism for palladium-catalyzed decarboxylative cyclization

As a related work, palladium-catalyzed reaction of an allyl-substituted 2*H*-azirine giving pyrrole and pyridine derivatives was also reported by Izumi and Alper.[13] They reported selective formation of a pyridine derivative as the only example of the selective reaction. When we performed a palladium-catalyzed reaction of an allyl-substituted 2*H*-azirine **5** under the present reaction conditions, the yield of pyrrole **3b** was only 32% (Scheme 5). This result indicates the high reactivity of the azirine itself for the intermolecular reactions or the self-dimerization reactions.[14–16]



Scheme 5. The palladium-catalyzed reaction starting from 2*H*-azirine **5**

The acetylenic tether of the isoxazolone substrate was also examined for the palladium-catalyzed decarboxylative transformation. As shown in Scheme 6, isoxazolone **6** also underwent the decarboxylation in the presence of a palladium catalyst to afford unstable α,β-unstaturated *N*-H imine **7**. Imine **7** was extremely unstable to the moisture and therefore converted to the corresponding acetamide **9** by the hydride reduction/acetylation sequence. Formation of imine **7** can be attributed to the β-hydride elimination in azapalldacyclobutene **E** (equivalent to imido complex **D**) that is followed by reductive elimination. Cyclization with the alkyne moiety might be disfavored due to this competing reaction affording α,β-unstaturated *N*-H imines.



Scheme 6. The palladium-catalyzed decarboxylative reaction of an alkyne-substituted isoxazolone

In conclusion, we have developed a selective and efficient synthetic method to access trisubstituted pyrroles via palladium-catalyzed decarboxylative cyclization of alkene-tethered isoxazol-5(4*H*)-ones. The selectivity towards pyrroles was greatly improved by using Buchwald's bulky biaryl-di-*t*-butylphosphine ligand (*t*-BuXphos). We have also proposed a reaction mechanism involving the generation of a nitrene–palladium complex that proceeds through N–O bond cleavage followed by decarboxylation. Deuterium-labeling experiments support a mechanism of pyrrole formation in which β-hydride elimination takes place from an aza-palladacyclobutane intermediate followed by reductive elimination from isomerized C–Pd–H or N–Pd–H.

EXPERIMENTAL

General Information. NMR spectra were recorded with a JEOL EX-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts are reported in δ units (ppm) referenced to $CDCl_3$ (δ 7.26 ppm for ^{1}H NMR and δ 77.00 ppm for ^{13}C NMR). IR spectra were recorded with an FTIR spectrometer (JASCO FT/IR-460 Plus). Melting points (mp) are uncorrected. High-resolution mass spectra (HRMS) were measured with JEOL JMX-SX 102A (FAB) and Thermo Fisher Exactive (ESI) instruments. 1,4-Dioxane was distilled under nitrogen over sodium and benzophenone. Isoxazolones **1** and **6** were prepared according to the reported procedure.[8] Analytical data are shown below. All other materials were purchased and used without further purification.

4-Allyl-4-methyl-3-phenylisoxazol-5(4*H*)-one (1b) [CAS 21943-76-0]

A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.63 (s, 3H), 2.69 (dd, J = 14.2, 8.0 Hz, 1H), 2.73 (dd, J = 15.0, 6.8 Hz, 1H), 5.06 (dd, J = 16.6, 1.0 Hz, 1H), 5.08 (dd, J = 9.3, 1.5 Hz, 1H), 5.49 (ddt, J = 16.6, 10.2, 7.3

Hz, 1H), 7.48 (t, *J* = 8.3 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.9, 41.0, 51.0, 120.9, 126.8, 127.8, 129.1, 129.9, 131.7, 168.0, 180.8.

4-Allyl-4-methyl-3-(2-naphthyl)isoxazol-5(4*H*)-one (1c)

A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.74 (s, 3H), 2.78 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.87 (dd, *J* = 14.2, 6.8 Hz, 1H), 5.07 (d, *J* = 17.1 Hz, 1H), 5.08 (d, *J* = 10.7 Hz, 1H), 5.48–5.58 (m, 1H), 7.53–7.64 (m, 2H), 7.85–7.96 (m, 4H), 8.17 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.2, 41.3, 51.1, 121.0, 123.0, 125.2, 127.1, 127.3, 127.9, 128.1, 128.8, 129.2, 129.9, 132.7, 134.6, 167.9, 180.1. IR (neat) 476, 559, 751, 821, 896, 992, 1122, 1199, 1455, 1553, 1791, 2980 cm^{-1}. HRMS (FAB) calcd for $C_{17}H_{16}NO_2$ $(M+H)^+$ 266.1181, found 266.1180.

4-Allyl-4-methyl-3-(4-(trifluoromethyl)phenyl)isoxazol-5(4*H*)-one (1d)

A white solid. Mp 45.2−46.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.65 (s, 3H), 2.71 (dd, *J* = 14.2, 7.3 Hz, 1H), 2.76 (dd, *J* = 14.2, 7.3 Hz, 1H), 5.06 (d, *J* = 17.6 Hz, 1H), 5.10 (d, *J* = 10.7 Hz, 1H), 5.47 (ddt, *J* = 17.1, 10.3, 7.3 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.7, 41.0, 50.8, 121.2, 123.4 (q, *J* = 272 Hz), 126.2 (q, *J* = 3.3 Hz), 127.2, 129.5, 131.2, 133.3 (q, *J* = 32.2 Hz), 167.0, 180.2. IR (KBr) 841, 850, 890, 931, 1066, 1118, 1172, 1325, 1796 cm^{-1}. HRMS (FAB) calcd for $C_{14}H_{13}F_3NO_2$ $(M+H)^+$ 284.0898, found 284.0900.

4-Allyl-4-methyl-3-(4-methoxyphenyl)isoxazol-5(4*H*)-one (1e)

A colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 3H), 2.71 (d, *J* = 8.3 Hz, 2H), 3.87 (s, 3H), 5.02–5.11 (m, 2H), 5.48 (ddt, *J* = 16.6, 10.7 Hz, 7.3 Hz, 1H), 6.98 (d, *J* = 9.3 Hz, 2H), 7.73 (d, *J* = 9.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 22.0, 41.1, 50.9, 55.4, 114.6, 120.1, 120.7, 128.4, 130.0, 162.2, 167.4, 181.0. IR (neat) 574, 597, 838, 886, 1034, 1116, 1172, 1258, 1310, 1457, 1519, 1608, 1792, 2980 cm^{-1}. HRMS (FAB) calcd for $C_{14}H_{16}NO_3$ $(M+H)^+$ 246.1330, found 246.1123.

4-Allyl-3,4-diphenylisoxazol-5(4*H*)-one (1f)

A white solid. Mp 67.0−68.0 °C. ^{1}H NMR ($CDCl_3$): δ 3.03 (dd, *J* = 13.2, 7.3 Hz, 1H), 3.32 (dd, *J* = 13.2, 7.3 Hz, 1H), 5.07 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.13 (d, *J* = 9.8 Hz, 1H), 5.52 (ddt, *J* = 17.6, 10.2, 7.3 Hz, 1H), 7.28–7.45 (m, 8H), 7.49 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 37.5, 58.8, 121.8, 126.3, 127.2, 127.3, 129.0, 129.1, 129.4, 129.7, 131.7, 134.3, 167.1, 178.7. IR (KBr) 640, 688, 767, 886, 936, 1165, 1443, 1497, 1800 cm^{-1}. HRMS (FAB) calcd for $C_{18}H_{16}NO_2$ $(M+H)^+$ 278.1181, found 278.1184.

4,4-Diallyl-3-phenylisoxazol-5(4*H*)-one (1g)

A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.73 (dd, *J* = 14.2, 7.3 Hz, 2H), 2.78 (dd, *J* = 14.2, 7.3 Hz, 2H), 5.06 (dd, *J* = 16.8, 1.5 Hz, 1H), 5.08 (d, *J* = 10.7 Hz, 1H), 5.49 (ddt, *J* = 16.1, 11.2, 7.3 Hz, 1H), 7.45–7.58 (m, 3H), 7.78 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 40.0, 56.5, 121.0, 126.7, 128.0, 129.2, 129.6, 131.7, 166.4, 179.8. IR (neat) 641, 692, 763, 885, 930, 992, 1080, 1188, 1266, 1446, 1644, 1796, 3083 cm^{-1}. HRMS (FAB) calcd for $C_{15}H_{16}NO_2$ $(M+H)^+$ 242.1181, found 242.1186.

4,4-Diallyl-3-propylisoxazol-5(4*H*)-one (1h)

A pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.03 (t, *J* = 7.3 Hz, 3H), 1.77 (sext, *J* = 7.8 Hz, 2H), 2.27 (t, *J* = 7.8 Hz, 2H), 2.38 (dd, *J* = 14.2, 7.8 Hz, 2H), 2.55 (dd, *J* = 14.2, 7.3 Hz, 2H), 5.16 (d, *J* = 10.8 Hz, 1H), 5.17 (d, *J* = 17.3 Hz, 1H), 5.51 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 14.0, 17.4, 29.1, 38.8, 55.8, 120.7, 129.8, 170.2, 179.7. IR (neat) 876, 930, 993, 1073, 1195, 1442, 1643, 1789, 2967 cm^{-1}. HRMS (FAB) calcd for $C_{12}H_{18}NO_2$ $(M+H)^+$ 208.1338, found 208.1340.

3a-Allyl-4,5-dihydronaphtho[1,2-*c*]isoxazol-3(3a*H*)-one (1i)

A white solid. Mp 43.4−44.2 °C. ^{1}H NMR ($CDCl_3$): δ 2.09 (ddd, *J* = 19.0, 12.7, 6.3 Hz, 1H), 2.33 (dd, *J* = 13.7, 5.4 Hz, 1H), 2.49 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.52 (dd, *J* = 12.7, 6.8 Hz, 1H), 3.00 (dd, *J* = 18.1, 5.9 Hz, 1H), 3.18 (ddd, *J* = 18.1, 12.2, 5.4 Hz, 1H), 5.09 (d, *J* = 16.6 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 5.68 (dq, *J* = 17.6, 7.8 Hz, 1H), 7.28 (t, *J* = 8.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.5, 27.4, 35.9, 48.5, 120.6, 123.5, 124.7, 127.0, 129.2, 129.3, 131.9, 137.6, 167.1, 179.1. IR (KBr) 743, 781, 855, 923, 1072, 1179, 1381, 1432, 1464, 1596, 1790 cm^{-1}. HRMS (FAB) calcd for $C_{14}H_{14}NO_2$ $(M+H)^+$ 228.1025, found 228.1027.

General experimental procedure for the palladium-catalyzed reaction of isoxazolones 1 (Tables 1 and 2). To a solution of $Pd(dba)_2$ (11.5 mg, 20 μmol) and a phosphine ligand (20 μmol or 40 μmol) in 1,4-dioxane (1.5 mL) was added isoxazolone **1** (0.20 mmol) and the mixture was stirred at 80–100 °C for 4–12 h. The reaction mixture was filtered through a pad of Florisil and the filtrate was concentrated under vacuum. The residue was chromatographed on Florisil (hexane/EtOAc = 20/1) to give **3** and/or **4**.

3,5-Dimethyl-2-phenylpyrrole (3b) [CAS 3274-53-1]

A pale yellow oil (27.8 mg, 0.162 mmol, 81% yield). ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 2.27 (s, 3H), 5.82 (d, *J* = 2.9 Hz, 1H), 7.16-7.20 (m, 1H), 7.36-7.37 (m, 4H), 7.78 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 12.9, 110.2, 116.4, 125.4, 125.8, 126.7, 127.4, 128.6, 133.8. HRMS (FAB) calcd for $C_{12}H_{14}N$ $(M+H)^+$ 172.1126, found 172.1121.

3,5-Dimethyl-2-naphthylpyrrole (3c)

A white solid (32.8 mg, 0.148 mmol, 74% yield). Mp 105−106 °C. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 6H), 5.87 (d, *J* = 2.4 Hz, 1H), 7.38–7.50 (m, 2H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 9.3 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.92 (br s, 1H). ^{13}C NMR (CDCl$_3$): δ 12.6, 13.0, 110.5, 117.1, 123.6, 124.9, 125.2, 126.3, 126.7, 127.6, 127.9, 128.1, 131.3, 131.5, 133.8. IR (KBr) 506, 635, 749, 790, 819, 851, 1262, 1508, 1586, 3436 cm^{-1}. HRMS (FAB) calcd for $C_{16}H_{16}N$ (M+H)$^{+}$ 222.1283, found 222.1282.

3,5-Dimethyl-2-(4-(trifluoromethyl)phenyl)pyrrole (3d)

A pale yellow oil (37.9 mg, 0.158 mmol, 79% yield). ^{1}H NMR (CDCl$_3$): δ 2.25 (s, 3H), 2.30 (s, 3H), 5.86 (s, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.86 (br s, 1H). ^{13}C NMR (CDCl$_3$): δ 12.7, 12.9, 111.0, 118.5, 124.4 (q, *J* = 270 Hz), 125.3, 125.6 (q, *J* = 3.7 Hz), 126.8 (q, *J* = 32.1 Hz), 128.9, 137.11, 137.13. IR (neat) 521, 636, 797, 841, 1013, 1069, 1109, 1165, 1262, 1327, 1411, 1530, 1615, 2928, 3388 cm^{-1}. HRMS (FAB) calcd for $C_{13}H_{13}F_3N$ (M+H)$^{+}$ 240.1000, found 240.0994.

3,5-Dimethyl-2-(4-methoxyphenyl)pyrrole (3e) [CAS 42456-02-0]

A pale yellow oil (23.2 mg, 0.115 mmol, 58% yield). ^{1}H NMR (CDCl$_3$): δ 2.18 (s, 3H), 2.27 (s, 3H), 3.82 (s, 3H), 5.80 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.71 (br s, 1H). ^{13}C NMR (CDCl$_3$): δ 12.2, 12.9, 55.3, 109.8, 114.1, 115.2, 126.6, 126.7, 126.8, 127.4, 157.6. HRMS (FAB) calcd for $C_{13}H_{16}NO$ (M+H)$^{+}$ 202.1232, found 202.1229.

2,3-Diphenyl-5-methylpyrrole (3f) [CAS 3274-32-6]

A pale yellow oil (37.4 mg, 0.160 mmol, 80% yield). ^{1}H NMR (CDCl$_3$): δ 2.35 (s, 3H), 6.04 (d, *J* = 2.9 Hz, 1H), 7.10-7.40 (m, 10H), 7.92 (br s, 1H). ^{13}C NMR (CDCl$_3$): δ□12.9, 109.0, 122.2, 125.5, 126.4, 126.8, 127.2, 128.17, 128.21, 128.3, 128.6, 133.5, 136.8. HRMS (FAB) calcd for $C_{17}H_{16}N$ (M+H)$^{+}$ 234.1283, found 234.1283.

3-Allyl-5-methyl-2-phenylpyrrole (3g) [CAS 79815-48-8]

A pale yellow oil (29.9 mg, 0.151 mmol, 76% yield). ^{1}H NMR (CDCl$_3$): δ 2.29 (s, 3H), 3.34 (d, *J* = 6.3 Hz, 2H), 5.03 (d, *J* = 10.2 Hz, 1H), 5.09 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.86 (d, *J* = 2.4 Hz, 1H), 6.01 (ddt, *J* = 17.1, 9.8, 6.3 Hz, 1H), 7.17-7.25 (m, 1H), 7.34-7.39 (m, 4H), 7.80 (br s, 1H). ^{13}C NMR (CDCl$_3$): δ□13.0, 31.1, 109.0, 114.7, 118.9, 125.8, 126.3, 127.0, 127.8, 128.6, 133.6, 138.4. HRMS (FAB) calcd for $C_{14}H_{15}N$ (M+H)$^{+}$ 197.1204, found 197.1205.

3-Allyl-5-methyl-2-propylpyrrole (3h)

A pale yellow oil (22.3 mg, 0.137 mmol, 68% yield). ^{1}H NMR (CDCl$_3$): δ 0.93 (t, *J* = 7.3 Hz, 3H), 3.12 (sextet, *J* = 7.3 Hz, 2H), 2.20 (s, 3H), 2.47 (t, *J* = 7.3 Hz, 2H), 3.12 (d, *J* = 6.3 Hz, 2H), 4.94 (d, *J* = 9.8 Hz, 1H), 5.03 (d, *J* = 17.1 Hz, 1H), 5.66 (d, *J* = 2.9 Hz, 1H), 5.86 (d, *J* = 2.4 Hz, 1H), 6.01 (ddt, *J* = 16.6, 9.8, 6.3 Hz, 1H), 7.41 (br s, 1H). ^{13}C NMR (CDCl$_3$): δ 12.9, 13.9, 23.6, 27.8, 30.6, 106.6, 113.8, 116.7, 125.0, 126.8, 138.9. IR (neat) 789, 908, 1457, 2930, 2959, 3375 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{18}N$ $(M+H)^+$ 164.1439, found 164.1434.

2-Methyl-4,5-dihydro-1*H*-benzo[*g*]indole (3i) [CAS 220446-73-1]

A pale orange oil (22.5 mg, 0.123 mmol, 61% yield). ^{1}H NMR (CDCl$_3$): δ 2.32 (s, 3H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.89 (t, *J* = 7.8 Hz, 2H), 5.79 (s, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.15 (m, 2H), 7.98 (br s, 1H). ^{13}C NMR (CDCl$_3$): δ 13.3, 21.9, 30.1, 106.2, 117.5, 120.8, 124.3, 126.36, 126.44, 128.2, 128.6, 129.5, 134.3. HRMS (FAB) calcd for $C_{13}H_{14}N$ $(M+H)^+$ 184.1126, found 184.1122.

The synthesis of (*E*)-2,6,6-trimethyl-1-phenylhept-2-en-4-yn-1-amine (8)

To a flame-dried 30 mL Schlenk tube were added toluene (2.0 mL), Pd(PPh$_3$)$_4$ (23.6 mg, 20 μmol), and 4-(4,4-dimethylpent-2-yn-1-yl)-4-methyl-3-phenylisoxazol-5(4*H*)-one (**6**; 53.9 mg, 0.20 mmol). After stirring at 80 °C for 4 h, the mixture was cooled to –78 °C and DIBAL (0.57 mL, 0.80 mmol) was added. The mixture was stirred at room temperature for 15 h and filtered through a pad of Florisil® and evaporated. The residue was subjected to Florisil® column chromatography (Hexane/AcOEt = 3/1) to give (*E*)-2,6,6-trimethyl-1-phenylhept-2-en-4-yn-1-amine (**8**; 22.9 mg, 0.10 mmol) in 50% yield.

(*E*)-2,6,6-Trimethyl-1-phenylhept-2-en-4-yn-1-imine (7)

Unstable compound **7** was characterized with the ^{1}H NMR spectrum measured after removing solvent from the mixture of the palladium-catalyzed reaction. ^{1}H NMR (400 MHz, 28.2 °C, CDCl$_3$): δ 1.28 (s, 9H), 2.22 (s, 3H), 5.77 (d, *J* = 1.5 Hz, 1H), 7.27–7.43 (m, 6H).

(*E*)-2,6,6-Trimethyl-1-phenylhept-2-en-4-yn-1-amine (8)

A pale yellow oil. ^{1}H NMR (400 MHz, 24.6 °C, CDCl$_3$): δ 1.26 (s, 9H), 1.73 (s, 3H), 4.51 (s, 1H), 5.73 (t, *J* = 1.4 Hz, 1H), 7.21–7.28 (m, 1H), 7.32 (d, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, 24.6 °C, CDCl$_3$): δ 16.1, 28.1, 31.2, 61.6, 76.4, 102.7, 105.5, 126.9, 127.1, 128.4, 143.2, 151.9. IR (neat) 756, 847, 913, 1028, 1203, 1266, 1361, 1453, 1597, 2968.

The synthesis of (*E*)-N-(2,6,6-trimethyl-1-phenylhept-2-en-4-yn-1-yl)acetamide (9)

To a test tube were added (*E*)-2,6,6-trimethyl-1-phenylhept-2-en-4-yn-1-amine (8.9 mg, 39 μmol), acetyl chloride (3.1 μL, 43 μmol), and MeCN (1.0 mL). After stirring at 90 °C for 2 h, the mixture was evaporated and subjected to Florisil® column chromatography (Hexane/AcOEt = 3/1) to give (*E*)-N-(2,6,6-trimethyl-1-phenylhept-2-en-4-yn-1-yl)acetamide (**9**; 8.5 mg, 32 μmol) in 81% yield.

(*E*)-*N*-(2,6,6-Trimethyl-1-phenylhept-2-en-4-yn-1-yl)acetamide (9)

A white solid. Mp 134.9–136.2 °C. ^{1}H NMR (400 MHz, 23.5 °C, $CDCl_3$): δ 1.25 (s, 9H), 1.79 (s, 3H), 2.02 (s, 3H), 5.51 (t, J = 0.91 Hz, 1H), 5.55 (d, J = 8.2 Hz, 1H), 5.72 (d, J = 8.2 Hz, 1H), 7.21–7.38 (m, 5H). ^{13}C NMR (100 MHz, 20.8 °C, $CDCl_3$): δ 17.4, 23.3, 28.2, 31.1, 58.7, 76.0, 103.7, 107.1, 127.4, 127.8, 128.8, 139.5, 147.1, 168.8. IR (neat) 765, 807, 871, 982, 1099, 1204, 1270, 1372, 1540, 1647, 1740, 2969, 3304 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{23}NNaO$ $(M+Na)^+$ 292.1672, found 292.1664.

ACKNOWLEDGEMENT

This work was supported financially by Grant-in-Aid for Scientific Research (C) from MEXT, Japan (Grant Number 17K05861).

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