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Palladium(II)-catalyzed tandem intramolecular aminopalladation of alkynylanilines and conjugate addition for synthesis of 2,3-disubstituted indole derivatives

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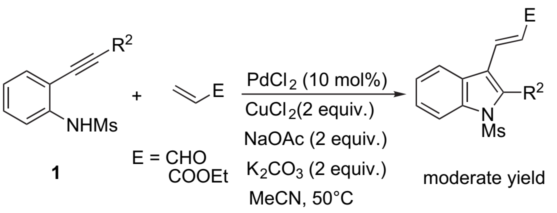
Abstract—An efficient method for the synthesis of 2,3-disubstituted indoles with high selectivity from 2-ethynylaniline derivatives and α,β-unsaturated carbonyl compounds was developed. This Pd(II)-catalyzed reaction involves tandem intramolecular aminopalladation, olefin insertion and protonolysis of the carbon-palladium bond with the regeneration of Pd(II) species in the presence of halide ions.

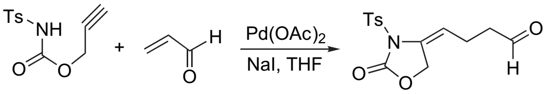
1. Introduction

The construction of the pyrrole ring incorporated into the indole system under the catalysis of the Pd complexes has been extensively studied.[1] The intramolecular cyclization of 2-ethynylaniline under the catalysis of Pd species belongs to one of the most useful methods for the systhesis of indoles.[1a] Yasuhara reported that the reaction of *N*-protected 2-alkynylanilines with electron-deficient alkenes in the presence of a palladium(II) catalyst and copper chloride as an oxidant in acetonitrile gave products of β-H elimination (Heck reaction), namely, 2-substituted 3-alkenylindoles with moderate yields (Eq. 1).[2]



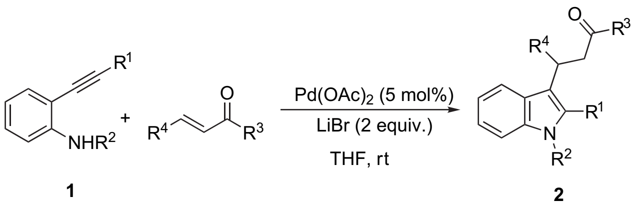
(1)

In our previous work, we reported the synthesis of oxazolidinones, imidazolidinones or lactams under the catalysis of a divalent palladium species with high chemo- and stereoselectivity from the intramolecular aminopalladation of alkynes, followed by insertion of acrolein, and finally, protonolysis of the newly formed-palladium bond (tandem aminopalladation and conjugate addition) (Eq. 2).[3] It is worth noting that in this reaction, the β-hydride elimination could be inhibited in the presence of an equivalent amount of NaI or LiBr.[4] Thus, the halide ions are crucial for this reaction.



(2)

Herein, we wished to report the Pd(II)-catalyzed reaction of 2-ethynylaniline with α,β-unsaturated carbonyl compounds in the presence of LiBr affording corresponding 2,3-disubstituted indoles without the occurrence of β-hydride elimination (Scheme 1).



Scheme 1. Tandem reaction of intramolecular aminopalladation and conjugate addition.

Keywords: Indole; Palladium; Aminopalladation; Conjugate addition.

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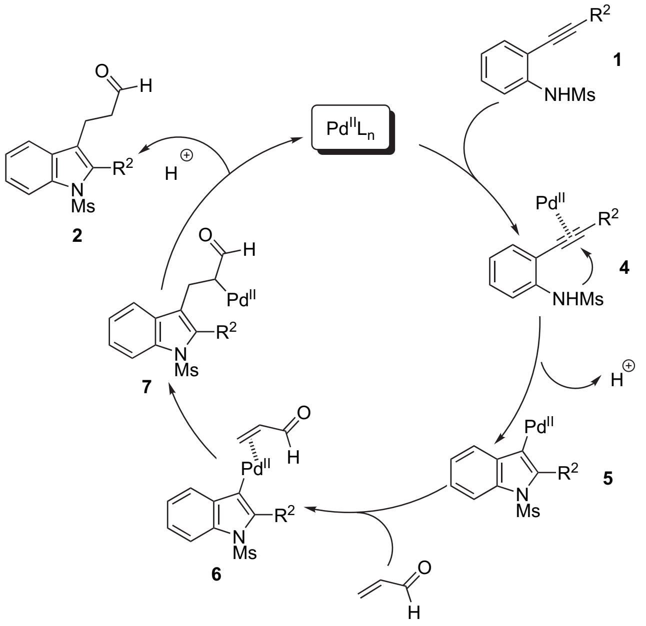
2. Results and discussion

The reaction conditions for the intramolecular aminopalladation of *N*-mesyl-2-ethynylaniline **1a** and the succeeding conjugate addition reaction with acrolein were examined as shown in Table 1.

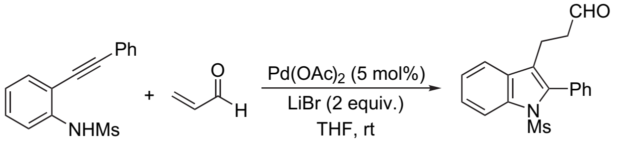
As a result, using 3 equiv of acrolein, the tandem reaction of 2-ethynylaniline proceeded smoothly in the presence of $Pd(OAc)_2$ (5 mol%) as catalyst and LiBr (2 equiv) as additive in THF at room temperature yielding the expected product **2a** in 85% yield without the occurrence of β-hydride elimination (Table 1, entry 2).

Under the same reaction conditions, different 2-ethynylaniline derivatives (**1b–1l**) and α,β-unsaturated carbonyl compounds were investigated as shown in Table 2. All the substrates with a sulfonyl group (tosyl or mesyl) on the nitrogen atom gave the good yield. It is worth noting that when the substituted group on nitrogen was trifluoroacetyl, acetyl or hydrogen, the reaction did not occur or gave a mixture of unknown products (Table 2, entries 4,7 and 10). This may be due to the requirement of a more acidic hydrogen on the nitrogen atom to facilitate the aminopalladation step.[3] For substrates with a variety of R^1 groups on the triple bond, including Ph, *n*-Bu, CH_2OCH_3 and even the bulky TMS group, the reaction could afford products in good to excellent yield (Table 2, entries 1–3, 5,6 and 8). However, the yield of the reaction greatly decreased for the substrates with a terminal alkyne (**1j**, Table 2, entry 9). Beside acrolein, the reaction of **1a** with crotonaldehyde gave the expected product **2a′** in 81% yield (Table 2, entry 11). In the meanwhile, the reaction of compound **1c** with methyl vinyl ketone afforded the product **2c′** in 76% yield (Table 2, entry 12).



Scheme 2. Mechanism of the reaction.

Table 1. Palladium(II)-catalyzed tandem reaction with different amounts of acrolein[a]

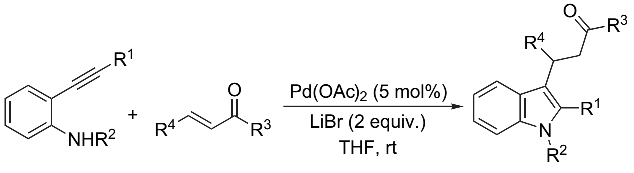


1a **2a**

Entry	Time (day)	Acrolein (equiv)	Yield (%)[b]
1	1	10	71
2	1	3.0	85
3	2	1.5	78

[a] Conditions: substrate **1a** (0.22 mmol), LiBr (2 equiv), THF (1.1 mL).
[b] Isolated yield.

Table 2. Palladium(II)-catalyzed tandem reaction for the synthesis of indoles from 2-alkynylaniline and α,β-unsaturated carbonyl compounds[a]



1 **2**

Entry	1	R^1	R^2	R^3	R^4	Time	Yield (%)[b]
1	**1b**	Ph	Ts	H	H	Overnight	83 (**2b**)
2	**1c**	*n*-Bu	Ts	H	H	Overnight	88 (**2c**)
3	**1d**	*n*-Bu	Ms	H	H	Overnight	75 (**2d**)
4	**1e**	*n*-Bu	Ac	H	H	6 d	Trace
5	**1f**	CH_2OCH_3	Ms	H	H	1 d	89 (**2f**)
6	**1g**	CH_2OCH_3	Ts	H	H	Overnight	94 (**2g**)
7	**1h**	CH_2OCH_3	$COCF_3$	H	H	5 d	N.R.
8	**1i**	TMS	Ms	H	H	4 d	72 (**2i**)
9	**1j**	H	Ms	H	H	3 d	27 (**2j**)
10	**1l**	Ph	H	H	H	5 d	Disordered
11	**1a**	Ph	Ms	H	CH_3	4 d	81 (**2a′**)
12	**1c**	*n*-Bu	Ts	CH_3	H	2 d	76 (**2c′**)

[a] Conditions: substrate **1a** (0.22 mmol), α,β-unsaturated carbonyl compounds (3 equiv), LiBr (2 equiv), THF (1.1 mL).
[b] Isolated yield.

The following mechanism is proposed for this reaction: first, the Pd(II) species will coordinate with the triple bond of the substrate **1**. Trans attack of mesyl or tosyl amide anion to the coordinated triple bond may afford indole palladium intermediate **5** (aminopalladation),[5] followed by insertion of the double bond of the acrolein and protonolysis of the newly formed carbon–palladium bond via the palladium enolate **7** in the presence of halide ions to yield aldehyde **2** and regenerate the divalent palladium species to complete the catalytic cycle (Scheme 2).[4b,6] The key point in this tandem reaction is that the halide ions can block the β-hydride elimination of a (2-oxoalkyl)-palladium species, giving preferentially the protonolysis product in acidic media.[4b] This also indicates the reason that a sulfonamide amino group (more acidic) is preferential for this reaction.

3. Conclusion

In summary, we developed an efficient method for the synthesis of 2,3-disubstituted indoles with high selectivity from 2-alkynylaniline derivatives and α,β-unsaturated carbonyl compounds. This Pd(II)-catalyzed reaction involves tandem intramolecular aminopalladation, olefin insertion and protonolysis of the carbon-palladium bond.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained on a Varian EM-360 at 300 and 75 MHz, respectively. The mass spectra were run using a Hewlett–Packard MS-Engine 5989A instrument. Infrared spectra were recorded on a Bio-Rad FTS-185 machine. 2-Ethynylaniline derivative **1a**–**1d**,[7] **1f**–**1g**,[7] **1i**,[7] **1g**,[7] **1e**,[8] **1h**[9] and **1j**[10] was prepared according to the literature. LiBr was purified according to the standard method.

4.2. General procedure for the reaction of 2-alkynylaniline derivatives with α,β-unsaturated carbonyl compounds under the catalysis of Pd(II)

A solution of **1** (0.22 mmol), LiBr (0.44 mmol), α,β-unsaturated carbonyl compounds (0.66 mmol), Pd(OAc)$_2$ (5 mol%, 2.5 mg) in dry THF (1.1 mL) was stirred under nitrogen at room temperature. After the reaction was finished as monitored by TLC, silica gel (100–200 mesh) was added into the mixture and the solvent was evaporated under reduced pressure. The residues were purified by flash chromatography on silica gel with petroleum ether–ethyl acetate (10/1–4/1 (v/v)) as the eluent to afford the white solid **2**.

4.2.1. 3-(*N*-Mesyl-2′-phenylindol-3′-yl)propanal (2a). White solid, 85% yield, mp: 135–137 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.64 (t, J=7.2 Hz, 2H), 2.83 (s, 3H), 2.91 (t, J=7.2 Hz, 2H), 7.35–7.48 (m, 7H), 7.55–7.58 (m, 1H), 8.12–8.15 (m, 1H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 16.8, 40.4, 43.4, 115.3, 119.0, 121.2, 124.1, 125.3, 128.0, 129.0, 129.7, 130.7, 130.8, 136.6, 136.9, 201.0; IR (KBr): ν 2932, 1714, 1450, 1355, 1171 cm^{-1}; MS (EI) *m/z*: 327 (M)$^+$, 271, 230, 218, 205, 204, 115, 55; Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 66.22; H, 5.30; N, 4.08.

4.2.2. 3-(*N*-Tosyl-2′-phenylindol-3′-yl)propanal (2b). White solid, 83% yield, mp: 159–160 °C (recrystallization from petroleum ether–ethyl acetate). ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.32 (s, 3H), 2.49–2.54 (m, 2H), 2.78–2.83 (m, 2H), 7.08 (d, J=8.1 Hz, 2H), 7.26–7.46 (m, 10H), 8.33–8.36 (m, 1H), 9.59 (t, J=1.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 16.8, 21.5, 43.3, 116.0, 118.7, 121.5, 123.8, 125.1, 126.7, 127.6, 128.8, 129.3, 129.9, 130.9, 131.1, 135.2, 136.97, 137.01, 144.5, 201.1; IR (KBr): ν 2836, 2737, 1720, 1366, 1172 cm^{-1}; MS (EI) *m/z*: 403 (M)$^+$, 402 (M−1)$^+$, 346, 230, 203, 91, 57, 56, 55; Anal. Calcd for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47. Found: C, 71.31; H, 5.38; N, 3.18.

4.2.3. 3-(*N*-Tosyl-2′-*n*-butylindol-3′-yl)propanal (2c). Oil, 88% yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.94 (t, J=7.2 Hz, 3H), 1.35–1.48 (m, 2H), 1.60–1.65 (m, 2H), 2.32 (s, 3H), 2.69 (t, J=7.8 Hz, 2H), 2.90–3.00 (m, 4H), 7.14 (d, J=8.1 Hz, 2H), 7.23–7.27 (m, 2H), 7.33–7.36 (m, 1H), 7.52–7.55 (m, 2H), 8.16–8.19 (m, 1H), 9.77 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.8, 16.6, 21.4, 22.7, 26.2, 33.1, 43.7, 115.4, 118.0, 119.1, 123.5, 124.1, 126.1, 129.6, 130.0, 135.8, 136.7, 138.3, 144.4, 201.1; IR (neat): ν 2959, 2929, 1724, 1454, 1365, 1174 cm^{-1}; MS (EI) *m/z*: 383 (M)$^+$, 382 (M−1)$^+$, 326, 155, 143, 115, 105, 91, 55; HRMS Calcd for $C_{22}H_{25}NO_3S$: 383.1555, found: 383.1566.

4.2.4. 3-(*N*-Mesyl-2′-*n*-butylindol-3′-yl)propanal (2d). White solid, 75% yield, mp: 62–63 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, J=7.2 Hz, 3H), 1.37–1.45 (m, 2H), 1.57–1.67 (m, 2H), 2.79 (t, J=6.9 Hz, 2H), 2.94 (s, 3H), 2.92–3.03 (m, 4H), 7.28–7.32 (m, 2H), 7.44–7.47 (m, 1H), 8.00–8.04 (m, 1H), 9.86 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.8, 16.6, 22.7, 25.9, 33.0, 40.0, 43.8, 114.6, 118.3, 118.7, 123.7, 124.4, 130.0, 136.3, 138.3, 201.1; IR (KBr): ν 3033, 2958, 1721, 1456, 1351, 1166 cm^{-1}; MS (EI) *m/z*: 307 (M)$^+$, 251, 222, 143, 130, 115, 55, 40; Anal. Calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.49; H, 7.00; N, 4.27.

4.2.5. 3-(*N*-Mesyl-2′-methoxymethylindol-3′-yl)propanal (2f). Oil, 89% yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.82 (t, J=7.5 Hz, 2H), 3.09 (m, 2H), 3.21 (s, 3H), 3.45 (s, 3H), 4.77 (s, 2H), 7.27–7.39 (m, 2H), 7.52–7.54 (m, 1H), 8.08 (d, J=7.5 Hz, 1H), 9.83 (t, J=0.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 16.3, 40.9, 44.0, 58.1, 63.4, 114.3, 119.1, 121.6, 123.3, 125.4, 128.5, 132.3, 136.3, 200.9; IR (neat): ν 2931, 1715, 1362, 1172 cm^{-1}; MS (EI) *m/z*: 295 (M$^+$), 172, 156, 144, 143, 142, 130, 115, 45; HRMS Calcd for ($C_{14}H_{17}NO_4S+Na^+$): 318.0770, found: 318.0775.

4.2.6. 3-(*N*-Tosyl-2′-methoxymethylindol-3′-yl)propanal (2g). White solid, 94% yield, mp: 112–114 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.32 (s, 3H), 2.75 (dt, J_1=0.9, J_2=7.2 Hz, 2H), 3.04 (t, J=7.2 Hz, 2H), 3.41 (s, 3H), 4.83 (s, 2H), 7.16–7.46 (m, 5H), 7.80–7.83 (m, 2H), 8.14–8.17 (m, 1H), 9.78 (t, J=0.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 16.6, 21.5, 44.0, 57.9, 63.5, 115.0, 118.9, 122.8, 123.3, 125.3, 126.9, 128.9, 129.4, 132.8, 135.8, 136.4, 144.5, 201.1; IR (KBr): ν 3065, 1716, 1368, 1179 cm^{-1}; MS (EI) *m/z*: 371 (M)$^+$, 370 (M−1)$^+$, 172, 156, 130, 115, 105, 91, 77, 45; HRMS Calcd for $C_{20}H_{21}NO_4S$: 371.1191, found: 371.1199.

4.2.7. 3-(*N*-Mesyl-2′-trimethylsilylindol-3′-yl)propanal (2i). Yellow solid, 72% yield, mp: 57–58 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.47 (s, 9H), 2.79 (s, 3H), 2.77–2.82 (m, 2H), 3.17–3.22 (m, 2H), 7.31–7.41 (m, 2H), 7.49–7.52 (m, 1H), 8.01–8.04 (m, 1H), 9.86 (t, J=1.2 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 2.3, 17.9, 38.4, 45.0, 114.8, 119.0, 123.8, 125.9, 131.7, 134.6, 137.6, 139.1, 200.7; IR (KBr): ν 3015, 2976, 2830, 1717, 1359, 1178 cm^{-1}; MS (EI) *m*/*z*: 323 (M$^+$), 154, 143, 137, 75, 73, 59, 45, 43; HRMS Calcd for C$_{15}$H$_{21}$NO$_3$SSi: 323.1011, found: 323.1021.

4.2.8. 3-(*N*-Mesyl-indol-3′-yl)propanal (2j). White solid, 27% yield, mp: 82–83 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.89 (t, J=7.2 Hz, 2H), 3.06 (s, 3H), 3.03–3.08 (m, 2H), 7.22 (s, 1H), 7.30–7.41 (m, 2H), 7.57 (d, J=8.1 Hz, 1H), 7.90 (d, J=8.1 Hz, 1H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 17.3, 40.4, 42.8, 113.2, 119.5, 121.2, 122.7, 123.4, 125.2, 130.4, 135.3, 200.9; IR (KBr): ν 3128, 3019, 2926, 1732, 1446, 1354, 1168 cm^{-1}; MS (EI) *m*/*z*: 251 (M$^+$), 195, 144, 143, 130, 116, 115, 55; HRMS Calcd for C$_{12}$H$_{13}$NO$_3$S: 251.0616, found: 251.0613.

4.2.9. 3-(*N*-Mesyl-2′-phenylindol-3′-yl)-3-methylpropanal (2a′). White solid, 81% yield, mp: 134–136 °C (recrystallization from petroleum ether–dichloromethane). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.38 (d, J=7.2 Hz, 3H), 2.73 (ddd, J_1=1.8, J_2=7.2, J_3=16.8 Hz, 1H), 2.88 (s, 3H), 2.85–2.93 (m, 1H), 3.36–3.44 (m, 1H), 7.33–7.49 (m, 7H), 7.69–7.72 (m, 1H), 8.14–8.17 (m, 1H), 9.56 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 20.7, 25.9, 40.7, 49.2, 115.4, 120.2, 123.7, 125.0, 128.0, 128.4, 129.1, 130.8, 131.1, 131.2, 136.0, 136.9, 201.1; IR (KBr): ν 3014, 2967, 1721, 1365, 1175 cm^{-1}; MS (EI) *m*/*z*: 341 (M)$^+$, 340 (M$-$1)$^+$, 219, 218, 187, 185, 135, 77, 40; HRMS Calcd for C$_{19}$H$_{19}$NO$_3$S: 341.1086, found: 341.1091.

4.2.10. 4-(*N*-Mesyl-2′-*n*-butylindol-3′-yl)but-2-one (2c′). White solid, 76% yield, mp: 62–63 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, J=7.5 Hz, 3H), 1.25–1.46 (m, 2H), 1.56–1.68 (m, 2H), 2.17 (s, 3H), 2.75 (t, J=7.8 Hz, 2H), 2.91–2.97 (m, 7H), 7.26–7.33 (m, 2H), 7.44–7.47 (m, 1H), 8.00–8.03 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.8, 18.1, 22.6, 25.8, 30.0, 33.0, 39.8, 43.3, 114.6, 118.4, 119.2, 123.6, 124.2, 130.2, 136.3, 138.1, 207.6; IR (KBr): ν 3035, 2952, 1714, 1351, 1165, 746 cm^{-1}; MS (EI) *m*/*z*: 321 (M)$^+$, 320 (M$-$1)$^+$, 222, 184, 156, 144, 143, 44, 43; HRMS Calcd for (C$_{17}$H$_{23}$NO$_3$S+Na$^+$): 344.1291, found: 344.1297.

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