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PALLADIUM-CATALYZED SYNTHESIS OF 2,2-DIMETHYL-3-PYRROLINES FROM α-AMINOALLENE AND ARYL IODIDES

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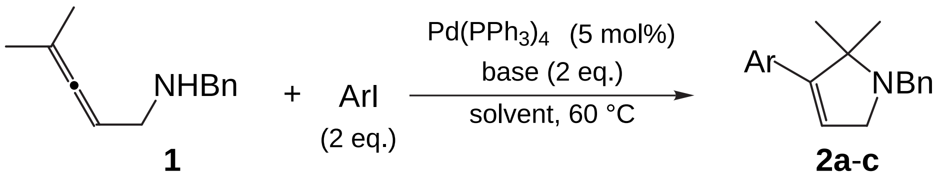
Abstract – Palladium-catalyzed cyclization of dimethyl-substituted allene possessing amino functionality with aryl iodides efficiently proceeded in the presence of diisopropylethylamine to give 2,2-dimethyl-3-aryl-3-pyrrolines. Under an atmospheric pressure of carbon monoxide, 3-aroyl-3-pyrrolines are provided in good yield.

Transition metal-catalyzed reaction using allenes as a three-carbon unit is a useful synthetic method.[1] In particular, palladium complex-catalyzed cyclizations of allenes by intramolecular heteronucleophilic attack is a fascinating route for the preparation of various heterocyclic compounds.[2] For example, the intramolecular reaction of aminoallenes with aryl halides catalyzed by palladium complex proceeds to give many kinds of nitrogen-containing ring systems.[3,4] Syntheses of 3-pyrrolines[5] from α-aminoallenes have been already reported[4b,f,g] but electron-withdrawing groups, like Ts and Mts (2,4,6-trimethylphenylsulfonyl), are used as a protecting group of amino moiety.

We here report that palladium complex-catalyzed cyclization of dimethyl-substituted α-aminoallenes with a benzyl group on nitrogen atom, which is easily deprotected. The choice of base is important for the high yield of products, 2,2-dimethyl-3-aryl-3-pyrrolines.[6] A reaction under an atmospheric pressure of carbon monoxide is also described.

We examined Pd(0) complex-catalyzed reaction of N-benzylallenylamine (**1**)[7] and iodobenzene using inorganic base (Table 1, entry 1). Allenylamine was not completely consumed and 3-pyrroline (**2a**) was obtained as an only detected product but in low yield. After screening of organic bases (entries 2-4), a bulky base was found to be best (entry 4). This is a rare example where diisopropylethylamine efficiently operated as a base in transition metal-catalyzed reactions.[8] 1,2-Dichloroethane (DCE) was also a preferable solvent (entry 5). In 1,2-dimethoxyethane (DME), **1** was readily consumed but to give **2a** in low yield (entry 6). Other aryl groups possessing electron-withdrawing or –donating group could be also introduced to pyrroline ring using 4-methoxyiodobenzene, 4-(ethoxycarbonyl)iodobenzene, respectively and **2b**,**c** were provided in good yield (entries 7,8).

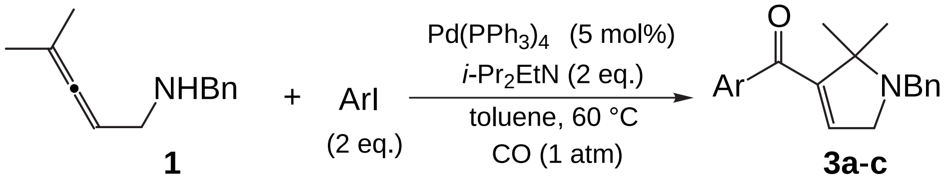
Table 1. Pd-catalyzed cyclization of α-aminoallene (**1**) with aryl iodide



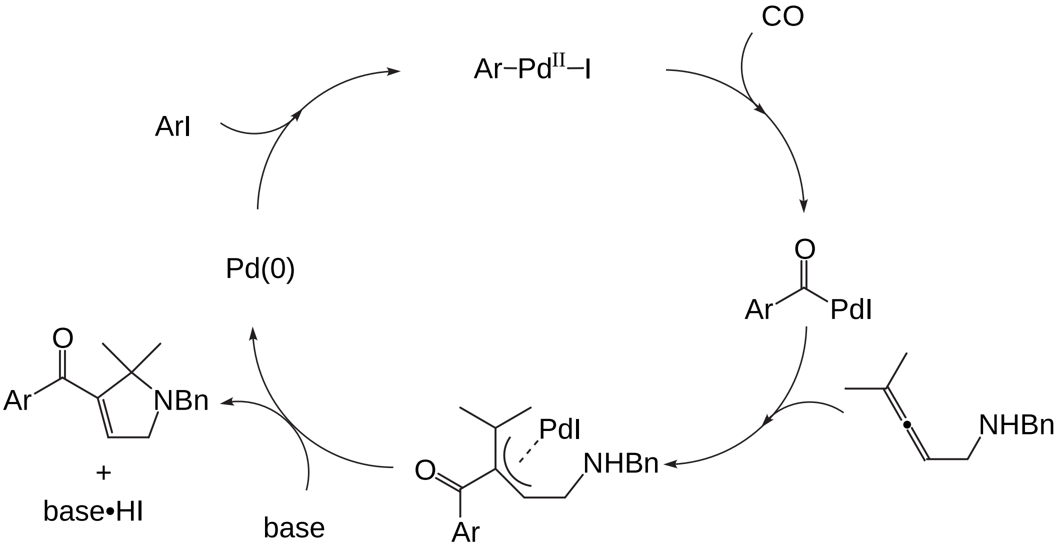
entry	Ar	base	solvent	time/h	yield/%
1	Ph	K_2CO_3	toluene	24	37 (**2a**)
2	Ph	2,6-lutidine	toluene	24	25 (**2a**)
3	Ph	Et_3N	toluene	12	66 (**2a**)
4	Ph	i-Pr_2EtN	toluene	15	82 (**2a**)
5	Ph	i-Pr_2EtN	DCE	11	79 (**2a**)
6	Ph	i-Pr_2EtN	DME	3	33 (**2a**)
7	4-$MeOC_6H_4$	i-Pr_2EtN	toluene	9	69 (**2b**)
8	4-$EtO_2CC_6H_4$	i-Pr_2EtN	toluene	7	73 (**2c**)

Next, the same reaction was examined under an atmosphere of carbon monoxide using three aryl iodides (Table 2). Aroyl group was introduced into 3-position of pyrroline ring and the corresponding 3-aroyl-2,2-dimethyl-3-pyrrolines (**3a-c**) were obtained in good yield. It is noteworthy that Pd-catalyzed carbonylative cyclization of aminoallenes smoothly proceeded under an atmospheric pressure of CO.[4g] Carbonylation of arylpalladium complex proceeds to give aroylpalladium complex prior to formation of π-allyl complex from allene.[9] The following cyclization by intramolecular nucleophilic attack of amine moiety to π-allyl complex provide 3- aroyl -3-pyrroline (Scheme 1).

Table 2. Pd-catalyzed carbonylative cyclization of α-aminoallene (**1**) with aryl iodide



entry	Ar	time/h	yield/%
1	Ph	9	73 (**3a**)
2	4-MeOC_6H_4	7	84 (**3b**)
3	4-Et$O_2CC_6H_4$	7	69 (**3c**)



Scheme 1

In conclusion, we synthesized 2,2-dimethyl-3-pyrrolines by palladium catalyzed cyclization of dimethyl-substituted α-aminoallene using a bulky organic base. At the 3-position of pyrrolines, aryl groups were introduced under an argon atmosphere and aroyl groups under an atmospheric pressure of CO.

EXPERIMENTAL

General. IR spectra were recorded with JASCO FT/IR-5000 spectrophotometer. ^{1}H NMR spectra (200 MHz) were measured with Varian VXR-200 spectrometer using tetramethylsilane (TMS) as an internal standard and $CDCl_3$ was used as solvent. HRMS spectra were obtained with JEOL JMS-SX102A mass spectrometer. Toluene was distilled from calcium hydride and degassed prior to use.

(4-Methylpenta-2,3-dienyl)benzylamine (1). 1 was prepared by the same procedure in the literature[10] from 1-bromo-4-methyl-2,3-pentadiene and benzylamine. Yellow oil; IR (neat) 2910, 1968, 1454, 1114 cm^{-1}; ^{1}H NMR δ= 1.71 (d, 6H, *J*= 2.8 Hz), 3.22 (d, *J*=6.2 Hz, 2H), 3.82 (s, 2H), 5.05-5.08 (m, 1H), 7.24-7.33 (m, 5H); HRMS found m/z 187.1349, calcd for $C_{13}H_{17}N$: 187.1361.

Typical experimental procedure for Pd-catalyzed cyclization (Table 1, entry 4). A mixture of $Pd(PPh_3)_4$ (13.1 mg, 0.011 mmol, 5 mol%), iodobenzene (103.2 mg, 0.453 mmol) and diisopropylethylamine (58.5 mg, 0.454 mmol) in toluene (2.5 mL) was stirred under an argon atmosphere for 30 min at 60 °C. A toluene solution (2.0 mL) of allene (**1**) (42.4 mg, 0.226 mmol) was added to the mixture, then the whole was stirred for 15 h at 60℃. The solvent was removed under reduced pressure and the crude products were purified by thin layer chromatography of silica gel (hexane/ethyl acetate=5/1) to give 3-pyrroline (**2a**) (49 .0 mg, 82%).

1-Benzyl-2,2-dimethyl-3-phenyl-3-pyrroline (2a). White solid; mp 36 °C (hexane); IR (neat) 1603, 1493, 1456, 1361 cm^{-1}; ^{1}H NMR δ= 1.33 (s, 6H), 3.38 (d, *J*= 2.2 Hz, 2H), 3.75 (s, 2H), 5.83 (t, *J*= 2.2 Hz, 1H), 7.24-7.43 (m, 10H); HRMS found m/z 263.1676, calcd for $C_{19}H_{21}N$: 263.1674.

1-Benzyl-2,2-dimethyl-3-(4-methoxyphenyl)-3-pyrroline (2b). Yellow solid; mp 82 °C (hexane); IR (neat) 1607, 1512, 1454, 1359, 1253 cm^{-1}; ^{1}H NMR δ= 1.35 (s, 6H), 3.38 (d, *J*= 2.1, 2H), 3.78 (s, 2H), 3.83 (s, 3H), 5.80 (t, *J*= 2.1 Hz, 1H), 6.90 (d, *J*= 8.8 Hz, 2H), 7.26-7.45 (m,7H); HRMS found m/z 293.1773, calcd for $C_{20}H_{23}NO$: 293.1780.

1-Benzyl-2,2-dimethyl-3-(4-ethoxycarbonylphenyl)-3-pyrroline (2c). Yellow solid; mp 92°C (hexane); IR (neat) 1717, 1607, 1456, 1376 cm^{-1}; ^{1}H NMR δ= 1.37 (s, 6H) , 1.41 (t, *J*= 7.2, 3H), 3.42 (d, *J* = 2.2 Hz, 2H), 3.77(s, 2H), 4.39 (q, *J*= 7.2 Hz, 2H), 5.98 (t, *J*= 2.2 Hz, 1H), 7.26-7.48 (m, 7H), 8.02 (d, *J*= 8.4 Hz, 2H); HRMS for (M+1) found m/z 336.1984, calcd for $C_{22}H_{26}NO_2$: 336.1965.

Typical experimental procedure for Pd catalyzed carbonylative cyclization (Table 2). It is the same procedure as above except the reaction was performed under an atmospheric presure of CO.

1-Benzyl-2,2-dimethyl(3-pyrroline-3-yl) phenyl ketone (3a). Yellow oil; IR (neat) 1644, 1325, 1241, 1170 cm^{-1}; ^{1}H NMR δ= 1.46 (s, 6H), 3.48 (d, *J* = 2.2 Hz, 2H), 3.79 (s, 2H), 6.40 (t, *J*= 2.2 Hz, 1H), 7.25-7.53 (m, 8H), 7.76 (d, *J*= 8.8 Hz, 2H); HRMS for (M+1) found m/z 292.1700, calcd for $C_{20}H_{22}NO$:

292.1703.

1-Benzyl-2,2-dimethyl(3-pyrroline-3-yl) 4-metoxyphenyl ketone (3b). Yellow oil; IR (neat) 1642, 1325, 1251, 1166 cm^{-1}; ^{1}H NMR δ= 1.44 (s, 6H), 3.47 (d, *J* =1.7 Hz, 2H), 3.72 (s, 2H), 3.86 (s, 3H), 6.33 (t, *J*= 1.7 Hz, 1H), 6.91 (d, *J*= 8.5 Hz, 2H), 7.26-7.41 (m, 5H), 7.80 (d, *J*= 8.5 Hz, 2H) ; HRMS found m/z 321.1727, calcd for $C_{21}H_{23}NO_2$: 321.1729.

1-Benzyl-2,2-dimethyl(3-pyrroline-3-yl) 4-ethoxycarbonylphenyl ketone (3c). Yellow oil; IR (neat) 1721, 1651, 1278 cm^{-1}; ^{1}H NMR **δ**= 1.40 (t, *J*= 7.1 Hz, 3H), 1.46 (s, 6H), 3.49 (d, *J* =2.0 Hz, 2H), 3.73 (s, 2H), 4.40 (q, *J*= 7.1 Hz, 2H), 6.40 (t, *J*= 2.0 Hz, 1H), 7.26-7.40 (m, 5H), 7.77 (d, *J*= 8.2 Hz, 2H), 8.09 (d, 2H); HRMS for (M+1) found m/z 364.1922, calcd for $C_{23}H_{26}NO_3$:364.1914.

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