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Pd(0)-Catalyzed Sequential Heck Reaction/C–H Activation/Amination with Diaziridinone: A Facile Approach to Indolines**

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Abstract

Indolines are important moieties present in various biologically significant molecules and have attracted considerable attention in synthetic chemistry. This paper describes a sequential Heck reaction/C–H activation/amination process to form indoline with di-*tert*-butyldiaziridinone. The reaction process likely proceeds via a pallada(II)cycle, which is converted to an indoline by oxidative addition to the diaziridinone and subsequent double C–N bond formation.

Keywords

indoline; Heck reaction; C–H activation; diaziridinone

Indolines are important moieties contained in various biologically and pharmaceutically active compounds,^[1] and their syntheses have attracted considerable attention. The cyclization involving replacement of a leaving group by a nitrogen is among widely used methods to synthesize indolines.^[2,3] Direct C–H amination presents an attractive strategy for the construction of this class of molecules and has become an active area in recent years.^[4–6]

Recently, we have reported that α -methylstyrene can be efficiently transformed to spirocyclic indolines via a Pd(0)-catalyzed sequential C–N bond formation involving allylic and aromatic C–H amination with di-*tert*-butyldiaziridinone (**1**) (Scheme 1).^[7] This reaction process likely proceeds via pallada(II)cycle **A**, which oxidatively inserts into the diaziridinone to form pallada(IV)cycle **B**.^[8] Upon release of *tert*-butyl isocyanate (*t*-BuNCO), intermediate **B** is converted to spirocyclic indoline **2** via two consecutive reductive eliminations.

Previously, we have shown that Pd(0) can readily insert into the N–N bond of diaziridinone **1**, and the resulting four-membered Pd(II) species reacts with dienes to form diamination products.^[9] The oxidative insertion of a pallada(II)cycle to di-*tert* butyldiaziridinone (**1**) is mechanistically interesting. To further probe this process, known pallada(II)cycle **3**^[10] was

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thus prepared^[11] and reacted with di-*tert*-butyldiaziridinone (**1**) (Scheme 2). The palladacycle was indeed smoothly transformed to indoline **4a** in 66% yield at room temperature.^[12] This result prompted us to investigate if the indoline could be directly formed from aryl halide (**5**), norbornene (**6a**), and di-*tert*-butyldiaziridinone (**1**) with catalytic amounts of Pd(0) by *in situ* formation of pallada(II)cycle **3** via Heck reaction and subsequent C–H activation (Scheme 3). The key issue for such transformation is whether aryl halide can compete with the diaziridinone for the oxidative addition by Pd(0) catalyst to initiate the catalytic cycle. Herein, we wish to report our preliminary studies on this subject.

Initial studies were carried out with *p*-iodoanisole (**5b**) as test substrate under various conditions. As shown in Table 1, the base had a significant effect on the reaction efficiency. No products were isolated with K₂CO₃, Na₂CO₃, and Et₃N (Table 1, entries 1–3). To our delight, the reaction proceeded efficiently with base such as K₃tPO₄, NaO Bu, and Cs₂CO₃ (Table 1, entry 4–6). For example, treating *p*-iodoanisole (**5b**) and norbornene (**6a**) with 1.5 equiv of di-*tert*-butyldiaziridinone (**1**), 10 mol% Pd(PPh₃)₄, and 2.0 equiv of Cs₂CO₃ in toluene at 80 °C gave indoline **4b** in 90% yield (Table 1, entry 6). Polar solvents such as DMF, MeCN, THF, and dioxane gave lower yields as compared to toluene (Table 1, entries 7–10). Similar yield (89%) was obtained when Pd(PPh₃)₄ was reduced from 10 mol% to 5 mol% (Table 1, entries 6 and 11). The effect of ligand was also briefly investigated with Pd₂(dba)₃ as catalyst (Table 1, entries 12–16). No product was formed with Pd₂(dba)₃ alone (Table 1, entry 12). PPh₃, P(*p*-MeO-Ph)₃, and P(*p*-CF₃-Ph)₃ were shown to be effective ligands for the reaction, giving indoline **4b** in 81–90% yield (Table 1, entry 13–15). However, no desired product was obtained with BINAP (Table 1, entry 16).

As shown in Table 2, the reaction process can be extended to various *para*-, *meta*-, *ortho*-, and disubstituted iodobenzenes, giving the corresponding indoline products in 67–97% yield (Table 2, entries 1–19). The Heck reaction occurred from the *exo* face of norbornene as indicated by the X-ray structure of **4g** (see Supporting Information). For bromo-substituted iodobenzenes **5d** and **5n**, the reaction selectively occurred on iodide and gave indolines **4d** and **4n** in good yields (Table 2, entries 4 and 14). For *meta*-substituted iodobenzenes (Table 2, entries 9–12 and entry 18), the C–H amination regioselectively occurred at the sterically less hindered position. Good yields (72–96%) were also obtained for the corresponding indolines (**7–9**)^[13] when norbornadiene (**6b**) and bridged olefins **6c**, **d** were used (Figure 1).^[14] As illustrated in the case of indoline **7b**, the reaction process is amenable to gram scale. Indoline **7b** can be converted to *N*-*tert*-butyl indole **10** in 79% yield with SiO₂ in xylenes via retro-Diels-Alder reaction and to tricyclic indoline **11** in 51% yield over 3 steps via dihydroxylation, oxidative diol cleavage, and reduction (Scheme 4).^[15] As shown in the case of indoline **4a**, the removal of the *tert*-butyl group was accomplished with CF₃SO₃H–cyclohexane, giving deprotected indoline **4a'** in 76% yield (Scheme 4).

The intramolecular reaction process was also found to be feasible with alkene-tethered iodobenzenes.^[16] As shown in Table 3, polycyclic fused indolines **13a–e**^[13] were readily obtained in 62–93% yield (Table 3, entries 1–5). Iodobenzenes bearing non-bridged 1,1-disubstituted olefins were also effective substrates for the reaction (Table 3, entries 2–5). When *o*-iodophenyl allyl ethers **14** with phenyl substituents on the olefins were subjected to

the reaction conditions, polycyclic spiro indolines **15** were obtained in 71–79% yield (Scheme 5). In these cases, the C–H activation occurred selectively at phenyl group **B** rather than phenyl group **A** to reduce the ring strain. Pentacyclic indoline **17** was obtained in 90% yield when iodobenzene **16** containing an exocyclic olefin was used as substrate (Scheme 6).^[17]

In summary, we have developed a novel Pd(0)-catalyzed sequential Heck reaction/C–H activation/amination process with iodobenzenes, olefins, and di-*tert*-butyldiaziridinone (**1**), providing a variety of polycyclic indolines in good yields. The reaction process likely proceeds via a pallada(II)cycle, which is intercepted by the diaziridinone via oxidative addition (Scheme 3). The resulting pallada(IV)cycle is transformed to the indoline product after release of *tert*-butyl isocyanate and subsequent reductive elimination. The current work not only provides a new approach to indolines, which are contained in various biologically important molecules, but also further illustrates the versatile reactivity and synthetic utility of diaziridinone, which may open up new opportunity for development of other reaction processes.

Experimental Section

Representative procedure for intermolecular process (Table 2, entry 1): To a 1.5 mL vial equipped with a magnetic stir bar were added iodobenzene (**5a**) (0.0612 g, 0.30 mmol), norbornene (**6a**) (0.0564 g, 0.60 mmol), di-*tert*-butyldiaziridinone (**1**) (0.0595 g, 0.35 mmol), Pd(PPh₃)₄ (0.0173 g, 0.015 mmol), Cs₂CO₃ (0.1956 g, 0.60 mmol), and toluene (0.30 mL, distilled from sodium). The vial was flushed with argon for 20 s, sealed, and then immersed into an oil bath (80°C). The reaction mixture was vigorously stirred at 80 °C for 48 h, cooled to room temperature, and purified by flash chromatography on silica gel (hexanes: ethyl acetate = 100:1) to give indoline **4a** (0.065 g, 90%).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. For selected examples, see: Bermudez J, Dabbs S, Joiner KA, King FD. *J. Med. Chem.* 1990; 33:1929. [PubMed: 2362271] Ontoria JM, Marco SD, Conte I, Francesco MED, Gardelli C, Koch U, Matassa VG, Poma M, Steinkühler C, Volpari C, Harper S. *J. Med. Chem.* 2004; 47:6443. [PubMed: 15588076] Abdel-Rahman AH, Keshk EM, Hanna MA, El-Bady Sh. M. *Bioorg. Med. Chem.* 2004; 12:2483. [PubMed: 15080944] Bentley JM, Adams DR, Bebbington D, Benwell KR, Bickerdike MJ, Davidson JEP, Dawson CE, Dourish CT, Duncton MAJ, Gaur S, George AR, Giles PR, Hamlyn RJ, Kennett GA, Knight AR, Malcolm CS, Mansell HL, Misra A, Monck NJT, Pratt RM, Quirk K, Roffey JRA, Vickers SP, Cliffe IA. *Bioorg. Med. Chem. Lett.* 2004; 14:2367. [PubMed: 15081042] Noguchi T, Tanaka N, Nishimata T, Goto R, Hayakawa M, Sugidachi A, Ogawa T, Asai F, Ozeki T, Fujimoto K. *Chem. Pharm. Bull.* 2007; 55:393. [PubMed: 17329879] Rode MA, Rindhe SS, Karale BK. *J. Serb. Chem. Soc.* 2009; 74:1377. Poondra RR, Kumar NN, Bijian K, Prakesch M, Campagna-Slater V, Reayi A, Reddy PT, Choudhry A, Barnes ML, Leek DM, Daroszewska M, Loughheed C, Xu B, Schapira M, Alaoui-Jamali MA, Arya P. *J. Comb. Chem.* 2009; 11:303. [PubMed: 19146410] Annedi SC, Ramnauth J, Maddaford SP, Renton P, Rakhit S, Mladenova G, Dove P, Silverman S, Andrews JS, Felice MD, Porreca F. *J. Med. Chem.* 2012; 55:943. [PubMed: 22175766]

2. For leading reviews on the synthesis of indolines, see: Anas S, Kagan HB. *Tetrahedron: Asymmetry*. 2009; 20:2193. Liu D, Zhao G, Xiang L. *Eur. J. Org. Chem.* 2010:3975. Zhang D, Song H, Qin Y. *Acc. Chem. Res.* 2011; 44:447. [PubMed: 21491859]
3. For leading reviews on C–N bond formation, see: Hartwig JF. *Angew. Chem. Int. Ed.* 1998; 37:2046. Wolfe JP, Wagaw S, Marcoux J-F, Buchwald SL. *Acc. Chem. Res.* 1998; 31:805. Yang BH, Buchwald SL. *J. Organomet. Chem.* 1999; 576:125. Ley SV, Thomas AW. *Angew. Chem. Int. Ed.* 2003; 42:5400. Evano G, Blanchard N, Toumi M. *Chem. Rev.* 2008; 108:3054. [PubMed: 18698737] Chemler SR. *J. Organomet. Chem.* 2011; 696:150. [PubMed: 21379363]
4. For recent leading reviews on C–H amination, see: Zalatan DN, Du Bois J. *Top. Curr. Chem.* 2010; 292:347. [PubMed: 21500412] Driver TG. *Org. Biomol. Chem.* 2010; 8:3831. [PubMed: 20617243] Cho SH, Kim JY, Kwak J, Chang S. *Chem. Soc. Rev.* 2011; 40:5068. [PubMed: 21643614] Ramirez TA, Zhao B, Shi Y. *Chem. Soc. Rev.* 2012; 41:931. [PubMed: 21842094] Gephart RT III, Warren TH. *Organometallics*. 2012; 31:7728. Roizen JL, Harvey ME, Bois J. *Du. Acc. Chem. Res.* 2012; 45:911. [PubMed: 22546004] Zhang L, Deng L. *Chin. Sci. Bull.* 2012; 57:2352. Jeffrey JL, Sarpong R. *Chem. Sci.* 2013; 4:4092.
5. For leading references on synthesis of indolines via sp^2 C–H activation, see: Houlden CE, Bailey CD, Ford JG, Gagné MR, Lloyd-Jones GC, Booker-Milburn KI. *J. Am. Chem. Soc.* 2008; 130:10066. [PubMed: 18613664] Li J-J, Mei T-S, Yu J-Q. *Angew. Chem. Int. Ed.* 2008; 47:6452. Wasa M, Yu J-Q. *J. Am. Chem. Soc.* 2008; 130:14058. [PubMed: 18834119] Mei T-S, Wang X, Yu J-Q. *J. Am. Chem. Soc.* 2009; 131:10806. [PubMed: 19606861] He G, Zhao Y, Zhang S, Lu C, Chen G. *J. Am. Chem. Soc.* 2012; 134:3. [PubMed: 22191666] He G, Lu C, Zhao Y, Nack WA, Chen G. *Org. Lett.* 2012; 14:2944. [PubMed: 22670815] Nadres ET, Daugulis O. *J. Am. Chem. Soc.* 2012; 134:7. [PubMed: 22206416] Mei T-S, Leow D, Xiao H, Laforteza BN, Yu J-Q. *Org. Lett.* 2013; 15:3058. [PubMed: 23725020]
6. For leading references on synthesis of indolines via sp^3 C–H activation, see: Larock RC, Hightower TR, Hasvold LA, Peterson KP. *J. Org. Chem.* 1996; 61:3584. [PubMed: 11667199] Watanabe T, Oishi S, Fujii N, Ohno H. *Org. Lett.* 2008; 10:1759. [PubMed: 18393521] Neumann JJ, Rakshit S, Dröge T, Glorius F. *Angew. Chem. Int. Ed.* 2009; 48:6892. Sun K, Sachwani R, Richert KJ, Driver TG. *Org. Lett.* 2009; 11:3598. [PubMed: 19627144] Rousseaux S, Davi M, Sofack-Kreutzer J, Pierre C, Kefalidis CE, Clot E, Fagnou K, Baudoin O. *J. Am. Chem. Soc.* 2010; 132:10706. [PubMed: 20681703] Nakanishi M, Katayev D, Besnard C, Kündig EP. *Angew. Chem. Int. Ed.* 2011; 50:7438. Nguyen Q, Sun K, Driver TG. *J. Am. Chem. Soc.* 2012; 134:7262. [PubMed: 22519742] Saget T, Lemouzy SJ, Cramer N. *Angew. Chem. Int. Ed.* 2012; 51:2238.
7. Ramirez TA, Wang Q, Zhu Y, Zheng H, Peng X, Cornwall RG, Shi Y. *Org. Lett.* 2013; 15:4210. [PubMed: 23919250]
8. For leading reviews on palladacycles derived from C–H activation, see: Dyker G. *Angew. Chem. Int. Ed.* 1999; 38:1698. Kakiuchi F, Chatani N. *Adv. Synth. Catal.* 2003; 345:1077. M. Catellani. *Synlett*. 2003:298. Alberico D, Scott ME, Lautens M. *Chem. Rev.* 2007; 107:174. [PubMed: 17212475] Catellani M, Motti E, Della Ca' N. *Acc. Chem. Res.* 2008; 41:1512. [PubMed: 18680317] Muñoz K. *Angew. Chem. Int. Ed.* 2009; 48:9412. Ackermann L, Vicente R, Kapdi AR. *Angew. Chem. Int. Ed.* 2009; 48:9792. Jazzar R, Hitce J, Renaudat A, Sofack-Kreutzer J, Baudoin O. *Chem. Eur. J.* 2010; 16:2654. [PubMed: 20143359] Xu L-M, Li B-J, Yang Z, Shi Z-J. *Chem. Soc. Rev.* 2010; 39:712. [PubMed: 20111789] Sehnal P, Taylor RJK, Fairlamb IJS. *Chem. Rev.* 2010; 110:824. [PubMed: 20143876] Shi F, Larock RC. *Top. Curr. Chem.* 2010; 292:123. [PubMed: 21500405] McMurray L, O'Hara F, Gaunt MJ. *Chem. Soc. Rev.* 2011; 40:1885. [PubMed: 21390391] Wencel-Delord J, Dröge T, Liu F, Glorius F. *Chem. Soc. Rev.* 2011; 40:4740. [PubMed: 21666903] Malinakova HC. *Top. Organomet. Chem.* 2011; 35:85.
9. a Du H, Zhao B, Shi Y. *J. Am. Chem. Soc.* 2007; 129:762. [PubMed: 17243803] b Du H, Yuan W, Zhao B, Shi Y. *J. Am. Chem. Soc.* 2007; 129:7496. [PubMed: 17521192] c Du H, Yuan W, Zhao B, Shi Y. *J. Am. Chem. Soc.* 2007; 129:11688. [PubMed: 17803307] d Du H, Zhao B, Shi Y. *J. Am. Chem. Soc.* 2008; 130:8590. [PubMed: 18549207] e Zhao B, Du H, Cui S, Shi Y. *J. Am. Chem. Soc.* 2010; 132:3523. [PubMed: 20166669]
10. a Catellani M, Ferioli L. *Synthesis*. 1996:769. b Catellani M, Frignani F, Rangoni A. *Angew. Chem. Int. Ed. Engl.* 1997; 36:119.
11. Chai DI, Thansandote P, Lautens M. *Chem. Eur. J.* 2011; 17:8175. [PubMed: 21647988]

12. For leading references on indoline formation from a nickel(II)cyclo and an azide, see: Koo K, Hillhouse GL. *Organometallics*. 1995; 14:4421. Koo K, Hillhouse GL. *Organometallics*. 1996; 15:2669.
13. The stereochemistry of compounds 8 and 13a were tentatively assigned by analogy to 7 and 4.
14. No reactions were observed when styrene and α -methylstyrene were used. It appears that the reaction might be facilitated by the strain of bicyclic olefins.
15. Thansandote P, Hulcoop DG, Langer M, Lautens M. *J. Org. Chem.* 2009; 74:1673. [PubMed: 19143500]
16. For leading references on tandem intramolecular Heck reaction/C–H activation processes, see: Huang Q, Fazio A, Dai G, Campo MA, Larock RC. *J. Am. Chem. Soc.* 2004; 126:7460. [PubMed: 15198591] Ruck RT, Huffman MA, Kim MM, Shevlin M, Kandur WV, Davies IW. *Angew. Chem. Int. Ed.* 2008; 47:4711. Lu Z, Hu C, Guo J, Li J, Cui Y, Jia Y. *Org. Lett.* 2010; 12:480. [PubMed: 20030345]
17. Bridged and 1,1-disubstituted olefins were used to avoid the β -hydride elimination.

Scheme 1.

The formation of spirocyclic indoline from α -methylstyrene.

Scheme 2.
Synthesis of indoline **4a** from pallada(II)cyclo **3**.

Scheme 3.
Proposed catalytic cycle.

Figure 1.
Indolines from other bridged olefins

Scheme 4.
Synthetic transformations of indolines **7b** and **4a**.

Scheme 5.
Synthesis of polycyclic spiro indoline **15**.

Scheme 6.
Synthesis of pentacyclic indoline **17**.

Table 1

Studies on the reaction conditions.^[a]

entry	solvent	base	catalyst	ligand	yield [%] ^[b]
1	PhMe	K ₂ CO ₃	Pd(PPh ₃) ₄	-	0
2	PhMe	Na ₂ CO ₃	Pd(PPh ₃) ₄	-	0
3	PhMe	Et ₃ N	Pd(PPh ₃) ₄	-	0
4	PhMe	K ₃ PO ₄	Pd(PPh ₃) ₄	-	79
5	PhMe	NaO ^t Bu	Pd(PPh ₃) ₄	-	82
6	PhMe	Cs ₂ CO ₃	Pd(PPh ₃) ₄	-	90
7	DMF	Cs ₂ CO ₃	Pd(PPh ₃) ₄	-	70
8	MeCN	Cs ₂ CO ₃	Pd(PPh ₃) ₄	-	84
9	THF	Cs ₂ CO ₃	Pd(PPh ₃) ₄	-	76
10	Dioxane	Cs ₂ CO ₃	Pd(PPh ₃) ₄	-	74
11 ^[c]	PhMe	Cs₂CO₃	Pd(PPh₃)₄	-	89
12	PhMe	Cs ₂ CO ₃	Pd ₂ (dba) ₃	-	0
13	PhMe	Cs ₂ CO ₃	Pd ₂ (dba) ₃	PPh ₃	84
14	PhMe	Cs ₂ CO ₃	Pd ₂ (dba) ₃	P(<i>p</i> -MeO-Ph) ₃	81
15	PhMe	Cs ₂ CO ₃	Pd ₂ (dba) ₃	P(<i>p</i> -CF ₃ -Ph) ₃	90
16	PhMe	Cs ₂ CO ₃	Pd ₂ (dba) ₃	BINAP	0

^[a] All reactions were carried out with *p*-iodoanisole (**5b**) (0.30 mmol), norbornene (**6a**) (0.60 mmol), di-*tert*-butyldiaziridinone (**1**) (0.45 mmol), Pd (0.030 mmol) (Pd/P = 1/4), base (0.60 mmol), and solvent (0.30 mL) at 80 °C under Ar for 36 h unless otherwise stated. For entry 4, the reaction time was 72 h.

^[b] Isolated yield.

^[c] The reaction was carried out with Pd(PPh₃)₄ (0.015 mmol) and di-*tert*-butyldiaziridinone (**1**) (0.35 mmol) at 80 °C for 48 h.

Table 2

Substrate scope.^[a]

entry	substrate (5)	product (4)	yield [%] ^[b]
1	5a , R = H	4a	90
2	5b , R = OMe	4b	89
3	5c , R = <i>n</i> -Bu	4c	91
4	5d , R = Br	4d	68
5	5e , R = F	4e	72
6	5f , R = CF ₃	4f	78
7	5g , R = CO ₂ Me	4g (X-ray)	93
8	5h , R = NO ₂	4h	84
9	5i , R = OMe	4i	82
10	5j , R = CH ₂ OTBS	4j	97
11	5k , R = CO ₂ Me	4k	85
12			84

entry	substrate (5)	product (4)	yield [%] ^[b]
13	5m , R = OMe	4m	90 ^[c]
14	5n , R = Br	4n	81 ^[c]
15	5o , R = NO ₂	4o	88 ^[c]
16	5p , R = OMe	4p	94 ^[c]
17	5q , R = NO ₂	4q	80 ^[c]
18			93
	5r	4r	
19			67
	5s	4s	

^[a] All reactions were carried out with iodobenzene **5** (0.30 mmol), norbornene (**6a**) (0.60 mmol), di-*tert*-butyl diaziridinone (**1**) (0.35 mmol), $\text{Pd(PPh}_3)_4$ (0.015 mmol), Cs_2CO_3 (0.60 mmol), and toluene (0.30 mL) at 80 °C under Ar for 48 h unless otherwise stated.

^[b] Isolated yield based on **5**.

^[c] Reaction time, 72 h.

Table 3

Intramolecular process.^[a]

entry	substrate	product	yield [%] ^[b]
1			93
	12a	13a	
2			75
	12b	13b	
3			65 ^[c,d]
	12c	13c (X-ray)	
4			81 ^[c]
	12d	13d	
5			62 ^[c]
	12e	13e (X-ray)	

^a All reactions were carried out with iodobenzene **12** (0.30 mmol), di-*tert*-butyldiaziridine (**1**) (0.35 mmol), Pd(PPh₃)₄ (0.015 mmol), Cs₂CO₃ (0.60 mmol), and toluene (0.30 mL) at 80 °C under Ar for 72 h unless otherwise stated.

^b Isolated yield based on compound **12**.

^c 0.030 mmol of Pd(PPh₃)₄ was used.

^d Reaction time, 120 h.