Monatsh Chem
DOI 10.1007/s00706-016-1819-2

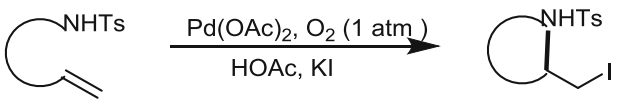
ORIGINAL PAPER

Palladium-catalyzed intramolecular aminoiodination of alkenes using molecular oxygen as oxidant

Lu Chen[1] · Xianglin Luo[1] · Yibiao Li[1]

Received: 27 May 2016 / Accepted: 11 July 2016

Abstract Molecular oxygen as oxidant to promote palladium-catalyzed intramolecular aminoiodination of alkenes has been described. The yields are excellent and show high *exo*-selectivities with various substrates.
Graphical abstract



Keywords Homogeneous catalysis · Heterocycles · Aminoiodination · Oxidations · Alkenes

Introduction

The development of general and efficient methodologies for the synthesis of complex molecular skeletons is the central focus of modern organic chemistry. Nitrogen heterocycles are common components of biologically active compounds [1, 2]. The halogenated nitrogen heterocycles have been applied as potential medicinal agents [3], and are primarily utilized to versatile synthetic intermediates [4–8]. Synthesis of nitrogen heterocycles via C–N bond formation represents a widely applied synthetic protocol [9, 10]. Therefore, the importance of the research for more direct and environmental friendly aminohalogenation modes is evident.

✉ Yibiao Li
wyuchemlyb@126.com

[1] School of Chemical and Environmental Engineering, Wuyi University, Jiangmen, China

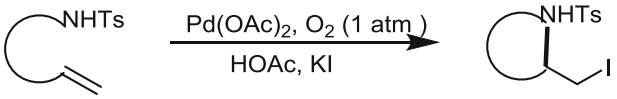
Transition-metal-catalyzed intramolecular aminohalogenation of alkenes remains relatively rare. Chemler reported that sulfonamidoalkenes could be cyclized with $Pd(TFA)_2$, using $CuCl_2$ (4 equiv) or $CuBr_2$ (3 equiv) as the halogen source and oxidant [11]. Lu described the cyclization of acylsulfonamides with $Pd(OAc)_2$ catalyst, also using copper halides as the halogen sources and oxidants [12]. Michael reported palladium-catalyzed intramolecular chloroamination of inactivated alkenes, using NCS as sources and oxidants [13]. Li described a novel and highly regioselective palladium-catalyzed intramolecular aminofluorination of alkenes using KI as the fluorinating reagent in the presence of $PhI(OPiv)_2$ [14]. On the other hand, the utilization of molecular oxygen as oxidant is one of the most important goals in oxidation chemistry [15–17]. Selective aerobic oxidation reactions constitute a broad class of important oxidative chemical transformations. As the "green oxidant", oxygen is an abundant, inexpensive, and thermodynamically potent oxidant. It would be preferred because it is environmentally benign and palladium-catalyzed aerobic oxidation reactions have been shown to be highly versatile in preparing fine chemicals [18–24]. Herein, we report molecular oxygen as oxidant to promote palladium-catalyzed intramolecular aminoiodination of alkenes.

Results and discussion

We firstly examined the intramolecular aminoiodination of 2-allyl-*N*-tosylaniline under different reaction conditions, and the results are summarized in Table 1. In the presence of the $Pd(OAc)_2$ catalyst (2 mol%), the reaction of 2-allyl-*N*-tosylaniline in HOAc at room temperature afforded **2a** in a 53 % yield and the β-hydride elimination product was not

Published online: 25 August 2016

Table 1 Optimization of reaction conditions



Entry	Atmosphere (1 bar)	Catalyst	Additive	Temp./°C	Yield/%[a]
1	O_2	$Pd(OAc)_2$	KI	r.t.	53
2	O_2	$Pd(OAc)_2$	KI	50	98 (94)
3	O_2	$Pd(OAc)_2$	KI	70	98
4	Air	$Pd(OAc)_2$	KI	50	72
5	N_2	$Pd(OAc)_2$	KI	50	<10
6	O_2	$Pd(OAc)_2$	NaI	50	92
7	O_2	$Pd(OAc)_2$	ZnI_2	50	88
8	O_2	$PdCl_2$	KI	50	76
9	O_2	$PdBr_2$	KI	50	84
10	O_2	$Pd_2(dba)_3$	KI	50	85
11	O_2	–	KI	50	<5
12	O_2	$FeCl_3$	KI	50	0

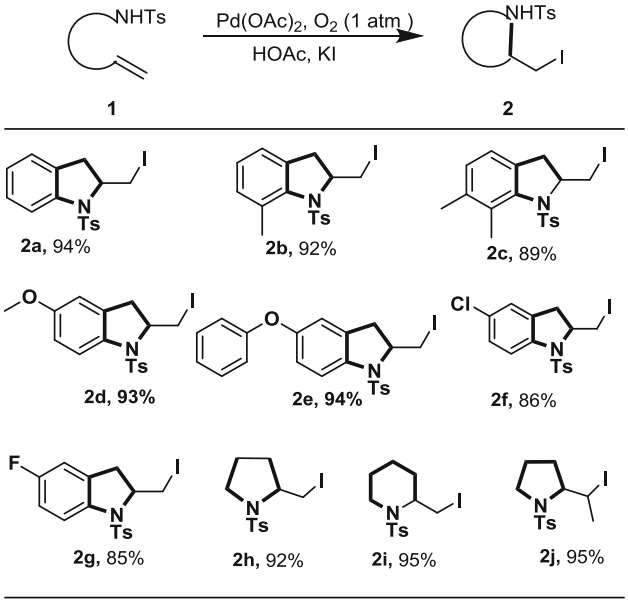
All reactions were performed with **1a** (0.25 mmol), catalyst (2 mol%), and additive (1.1 equiv) in 2 cm^3 of HOAc for 18 h

[a] Determined by GC. Number in parentheses is isolated yield

detected in this process (Table 1, entry 1) [25]. But high yield of *β*-hydride elimination product could be obtained if using other solvents (e.g., CH_3CN, DMF, DMSO, or 1,4-dioxane). The activity of substrate **1a** was improved significantly by raising temperature to 50 °C. By comparison with room temperature, higher temperature led to the same result (Table 1, entries 1–3). Using air as the oxidant led to an unsatisfactory yield (Table 1, entry 4). Only trace amounts of the desired product **2a** was obtained when reaction in nitrogen atmosphere (Table 1, entry 5). Further investigation on other iodide salts led to the inferior results, which indicated that the KI is the best choice (Table 1, entries 2 vs. 6, 7). Different palladium species were also tested, such as $PdCl_2$, $Pd_2(dba)_3$, $PdBr_2$, but the reaction did not proceed well (Table 1, entries 8–10). A Pd(0) complex could also be employed, as it is presumably oxidized to Pd(II) species under the oxidation reaction condition (Table 1, entry 10). Moreover, trace product of intramolecular aminoiodination was obtained without $Pd(OAc)_2$ (Table 1, entry 11). Under N_2 atmosphere, when $FeCl_3$ is utilized as catalyst instead of palladium salts, the intramolecular aminoiodination reaction did not give the desired product at all (Table 1, entry 12).

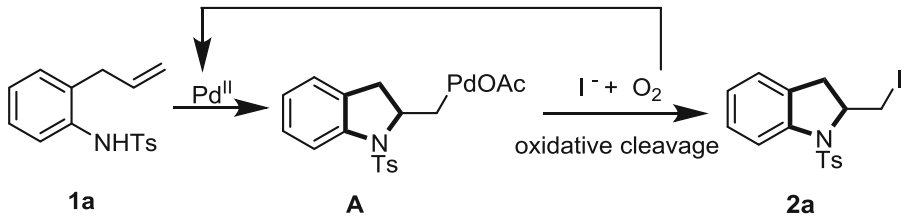
With the optimized conditions in hand, various substrates were examined, and the results are summarized in Scheme 1. In all the cases tested, the aminoiodination went smoothly, giving a good yield of the desired products. A series of the aniline-derived substrates with electron-rich substituents in the *para, meta*, or *ortho* position

Scheme 1

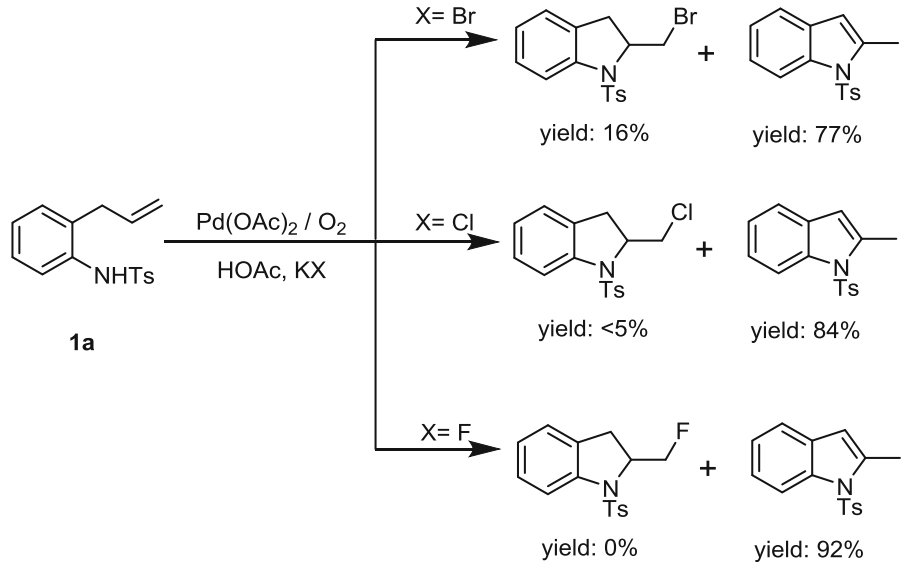


participation in reaction to give the corresponding aminoiodination products in higher yields in contrast to the case with electron-poor in the *para* position (**2a**-**2 g**). The reaction tolerated a variety of substituents including –Me, –MeO, –Cl, and –F groups. Substituents at the *ortho* position of benzyl group did not affect the yield of the reaction (**2b** and **2c**). Except the aniline-derived substrates, the aliphatic

Scheme 2



Scheme 3



alkenes were also found to be suitable substrates for the standard conditions. The pyrrolidines were readily synthesized from alkenylsulfonamides in high yields (**2h** and **2j**). A six-membered ring, piperidine **2i**, was also obtained in good yield by this procedure. Herein, simple filtration through a silica-gel plug was sufficient to remove the residual catalyst and provide desired piperidine products.

The exact pathways remain unknown at the present stage. In principle, intermediate **A** was formed from the intramolecular trans-nucleopalladation to **1a** activated by the palladium(II) species [9, 12, 26, 27]. Then followed by the cleavage of the carbon–palladium bond by I^- and O_2 result in **2a** (Scheme 2).

We next pursued analogous palladium-catalyzed intramolecular aminohalogenation of **1a** using KBr, KCl, and KF as halogen sources (Scheme 3). However, treatment of **1a** under the optimized conditions with KBr, KCl, or KF did not afford the expect results. Instead, the corresponding of β-hydride elimination product was obtained in high isolated yields. This result suggests that β-hydride elimination is significantly faster than C–X (X = Br, Cl, F) coupling in this system.

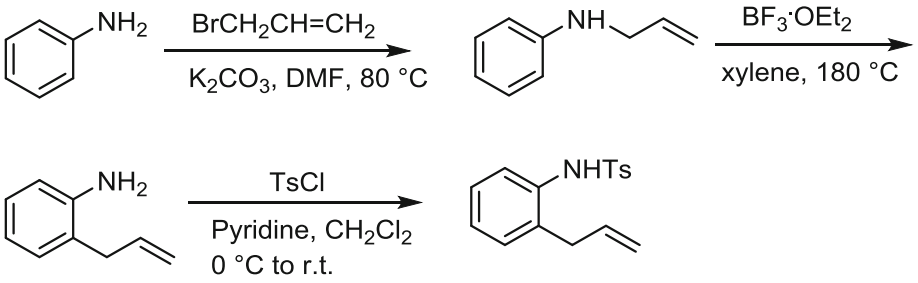
Conclusion

In conclusion, we have successfully developed palladium-catalyzed intramolecular aminoiodination of alkenes using molecular oxygen as oxidant. This process utilized molecular oxygen as sole oxidant to synthesis of various nitrogen heterocyclic rings. Moreover, the reaction condition was extremely mild and tolerated various functional groups, this will make this method of use to medicinal and academic chemists. Further studies on the mechanism, the scope of the reaction, and the potential for asymmetric induction in the aminoiodination process are in progress.

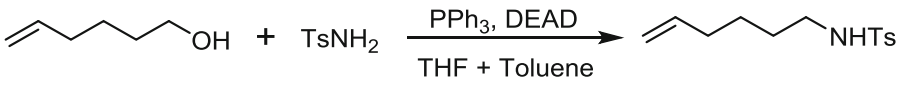
Experimental

Unless otherwise noted, all commercial materials and solvents were used without further purification. ^{1}H NMR spectra were recorded in $CDCl_3$ at 400 MHz (or BRUKER DRX-600 spectrometer) and ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 MHz, respectively. GC–MS was obtained using electron ionization. HRMS was carried out

Scheme 4



Scheme 5



on a MAT 95XP (Thermo). TLC was performed using commercially prepared 100–400 mesh silica gel plates (GF254), and visualization was effected at 254 nm. All the other chemicals were purchased from Alfa or Aldrich Chemicals. Commercial reagents were used without further purification. A typical procedure for the synthesis of amides [28] is shown in Scheme 4, a procedure for the synthesis of 2-allylanilines [29] in Scheme 5.

General procedure for aminoiodination of alkenes

The mixture of 2-allyl-*N*-tosylaniline (**1a**, 0.25 mmol), 46 mg KI (0.275 mmol), 1.1 mg $Pd(OAc)_2$ (0.005 mmol), and 2 cm^3 AcOH were mixed in a glass vial or round-bottom flask equipped with a magnetic stirring bar. The vial was flushed with oxygen and then connected to a balloon filled with oxygen. After rapid stirring at 50 °C for 18 h, the resulting crude oil was dissolved in 8 cm^3 ethyl acetate and washed with water (2 × 5 cm^3) and saturated aqueous $NaHCO_3$ (2 × 10 cm^3). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford a crude product, which was purified by chromatography on a silica gel column using light petroleum ether/ethyl acetate as eluent.

*2-(Iodomethyl)-1-tosylindoline (**2a**)*

Yield 94 %; m.p.: 154–156 °C (Ref. [14]).

*2-(Iodomethyl)-7-methyl-1-tosylindoline (**2b**)*

Yield 92 %; m.p.: 102–104 °C (Ref. [14]).

2-(Iodomethyl)-6,7-dimethyl-1-tosylindoline
(**2c**, $C_{18}H_{20}INO_2S$)

Yield 89 %; pale yellow solid; m.p.: 128–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.00 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 2.71–2.83 (m, 2H), 3.24 (t, J = 12.4 Hz, 1H), 3.59–3.67 (m, 1H), 4.26–4.36 (m, 1 H), 7.00 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.4, 15.7, 19.5, 21.5, 34.4, 62.4, 117.8, 126.9, 127.7, 129.3, 129.6, 133.2, 134.4, 136.3, 139.0, 144.0 ppm; HRMS (EI): *m/z* calcd for $C_{18}H_{20}INO_2S$ 441.0259, found 441.0252.

*2-(Iodomethyl)-5-methoxy-1-tosylindoline (**2d**)*

Yield 93 %; m.p.: 149–150 °C (Ref. [14]).

2-(Iodomethyl)-5-phenoxy-1-tosylindoline
(**2e**, $C_{22}H_{20}INO_3S$)

Yield 94 %; colorless crystalline solid; m.p.: 148–149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.38 (s, 3 H), 2.72–2.84 (m, 2H), 3.27 (t, 1H), 3.60 (dd, J = 3.6, 3.6 Hz, 1H), 4.38–4.57 (m, 1H), 6.56 (d, 1H), 6.85–6.87 (m, 1H), 6.94–6.98 (m, 1H), 7.00–7.08 (m, 1H), 7.20 (d, 2H), 7.22–7.24 (m, 2H), 7.55–7.61 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.5, 21.7, 34.9, 62.9, 116.0, 118.0, 118.6, 118.7, 123.4, 127.2, 129.9, 132.6, 134.2, 136.8, 144.4, 154.8, 157.3 ppm; HRMS (EI): *m/z* calcd for $C_{22}H_{20}INO_3S$ 505.0209, found 505.0201.

*5-Chloro-2-Iodomethyl-1-(p-toluenesulfonyl)-2,3-dihyro-1H-indole (**2f**)*

Yield 86 %; m.p.: 108–110 °C (Ref. [14]).

*5-Fluoro-2-(iodomethyl)-1-tosylindoline (**2g**)*

Yield 85 %; m.p.: 113–114 °C (Ref. [14]).

*2-(Iodomethyl)-1-tosylpyrrolidine (**2h**)*

Yield 92 %; m.p.: 92–93 °C (Ref. [7]).

*2-(Iodomethyl)-1-tosylpiperidine (**2i**)*
Yield 95 %; m.p.: 92–93 °C (Ref. [7]).

*2-(1-Iodoethyl)-1-tosylpyrrolidine (**2j**)*
Yield 95 %; m.p.: 112–114 °C (Ref. [7]).

Acknowledgments We thank the National Natural Science Foundation of China (21302146) and Science Foundation for Young Teachers of Wuyi University (2015td01).

References

1. Hegedus LS (1991) In: Trost BM, Fleming I (eds), Comprehensive Organic Synthesis, chapter 3.1. Permagon Press, New York
2. Spillane W, Malaubier JB (2014) Chem Rev 114:2507
3. Qiu J, Silverman RB (2010) J Med Chem 43:706
4. Kemp JEG (1991) In: Trost BM, Fleming I (eds) Comprehensive organic synthesis, vol 7. Permagon Press, Oxford, p 469
5. Tekkam S, Alam MA, Jonnalagadda SC, Mereddy VR (2011) Chem Commun 47:3219
6. Luo Y, Lu X, Ye Y, Guo Y, Jiang H, Zeng W (2012) Org Lett 14:5640
7. Minakata S, Morino Y, Oderaotoshi Y, Komatsu M (2006) Org Lett 8:3335
8. Tan CK, Yeung YY (2013) Chem Commun 49:7985
9. Minatti A, Muniz K (2007) Chem Soc Rev 36:1142
10. Li Y, Zhao J, Chen H, Liu B, Jiang H (2012) Chem Commun 48:3545
11. Manzoni MR, Zabawa TP, Kasi D, Chemler SR (2014) Organometallics 23:5618
12. Lei AW, Lu XY, Liu GS (2004) Tetrahedron Lett 45:1785
13. Michael FE, Sibbald PA, Cochran BM (2008) Org Lett 10:793
14. Liu GQ, Li YM (2014) J Org Chem 79:10094
15. Punniyamurthy T, Velusamy S, Lqbal J (2005) Chem Rev 105:2329
16. Popp BV, Stahl SS (2009) Chem Eur J 15:2915
17. Piera J, Backvall JE (2008) Angew Chem Int Ed 47:3506
18. Sheldon RA, Arends IWC, Brink GJ, Dijksman A (2002) Acc Chem Res 35:774
19. Ingram AJ, Walker KL, Zare RN, Waymouth RM (2015) J Am Chem Soc 137:13632
20. Izawa Y, Pun D, Stahl SS (2011) Science 333:209
21. Beccalli EM, Broggini G, Martinelli M, Sottocornola S (2007) Chem Rev 107:5318
22. Yeung CS, Dong VM (2011) Chem Rev 111:1215
23. Lyons TW, Sanford MS (2010) Chem Rev 110:1147
24. Decharin N, Popp BV, Stahl SS (2011) J Am Chem Soc 133:13268
25. Larock RC, Hightower TR, Hasvold LA, Peterson KP (1996) J Org Chem 61:3584
26. Trost BM, Vranken DLV (1992) Angew Chem Int Ed 31:228
27. Tamaru Y, Kimura M (1997) Synlett 749
28. Correa A, Tellitu I, Dominguez E, SanMartin R (2006) J Org Chem 71:8316
29. Kan T, Fujiwara A, Kobayashi H, Fukuyama T (2002) Tetrahedron 58:6276