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Palladium-Catalyzed Intermolecular Oxidative Diazidation of Alkenes

Haihui Peng, Zheliang Yuan, Pinhong Chen, and Guosheng Liu*

State Key Laboratory of Organometallics Chemistry, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, Shanghai 200032, China

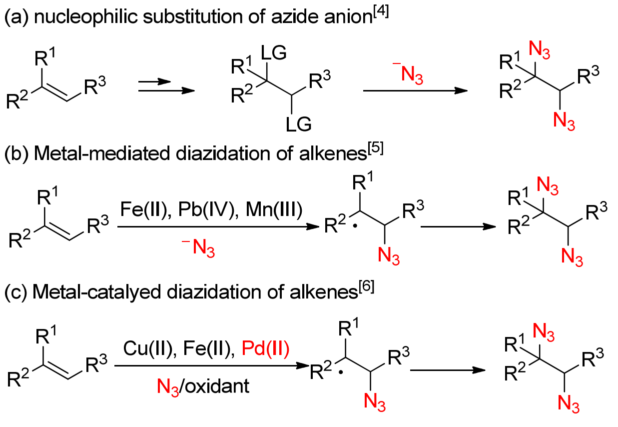
A palladium-catalyzed oxidative vicinal diazidation of alkenes has been developed, in which $TMSN_3$ was used as azide source. Both styrenes and unactivated alkenes are suitable for this reaction. And *trans*-alkyldiazides were obtained as major products from cyclic alkenes with moderate to good diastereoselectivities. This reaction afforded an efficient way for the synthesis of useful 1,2-diamines after hydrogenation.

Keywords palladium-catalyzed, azidation, alkene, styrene

Introduction

Organoazides are important organic compounds and valuable intermediates in organic synthesis.[1] Among them, 1,2-diazides are of crucial importance as precursors for the synthesis of valuable 1,2-diamines, which are prevalent in bioactive compounds and drugs.[2] So far, the realm of selective alkenes diazidation has still been underdeveloped. Traditional S_N2 displacements with nucleophilic azide anion is a mostly used way to 1,2-diazides albeit with lower efficiency and multi-steps (Scheme 1a).[3] Direct diazidation of alkenes represented an efficient approach to vicinal alkyl diazides. As far back as 1962, Minisci *et al.*[4] described a Fe(II)-mediated diazidation of alkenes using sodium azide. Similar reactions were also achieved with Pb(IV), Mn(III) as stoichiometric oxidant (Scheme 1b).[5] Recently, catalytic reactions with more environment-benign oxidant were reported.[6] Greaney *et al.*[6a] reported a Cu(I)-catalyzed diazidation of styrenes with iodine(III)-based azides (Zhdankin reagent). Xu *et al.*[6c] reported a Fe(II)-catalyzed diazidation of alkenes with $TNSN_3$ as the azide source and PhIO as the oxidant (Scheme 1c). These reactions are usually initiated with the generation of an azido radical under oxidative condition, then the azido radical adds to alkene to yield a carbon radical which is quenched by another azido radical or metallo-azido species to produce the alkyl diazide products. In these reactions, the diastereoselectivity is still a challenging issue in the case of internal alkenes. We have successfully accessed a serial of difunctionalization of alkenes via high valent palladium intermediates.[7] Recently, we reported a highly selective Pd-catalyzed fluorosulfonylation of styrenes, in which the ligated high valent palladium cation could act as an oxidant to generate the sulfonyl radical, and the recombination of a generated benzylic radical with the steric bulky palladium species exhibited a good diastereoselectivity.[7a] We envisioned that this strategy might be applied to the diazidation reaction. Herein, we reported a Pd-catalyzed oxidative vicinal diazidation of alkenes using $TMSN_3$ as an azide source, in which the tuning of diastereoselectivity from moderate to good could be achieved by addition of water.

Scheme 1 Diazidation of alkenes



Experimental

General procedure for palladium-catalyzed diazidation of styrenes

In a dried glass tube, $Pd(OTFA)_2$ (5.3 mg, 0.015

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* E-mail: gliu@mail.sioc.ac.cn; Tel.: 0086-021-54925346
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In Memory of Professor Enze Min.

mmol), $\mathbf{L}_1$ (10.8 mg, 0.023 mmol), NFSI (365.0 mg, 1.0 mmol) were dissolved in DMF (1.3 mL), and then styrene **1** (0.5 mmol) and $TMSN_3$ (1.5 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 1—3 h. After the reaction was completed, the solvent was extracted with hexane. After dried over Mg_2SO_4, the organic solvent was removed under vacuum, and the residue was purified by silica gel column chromatography with a gradient eluent of petroleum ether and ethyl acetate to afford pure products.

General procedure for palladium-catalyzed diazidation of unactivated alkenes

In a dried glass tube, $Pd(OTFA)_2$ (8.5 mg, 0.025 mmol), $\mathbf{L}_1$ (12.5 mg, 0.038 mmol), NFSI (365.0 mg, 1.0 mmol) and *p*-nitrobenzoic acid (255 mg, 1.5 mmol) were dissolved in 1,4-dioxane (1.3 mL), and then unactivated alkene **1** (0.5 mmol) and $TMSN_3$ (1.5 mmol) were added. The reaction mixture was stirred at room temperature for 1—3 h. After the reaction was completed, the mixture proceeded with the same workup to afford pure products.

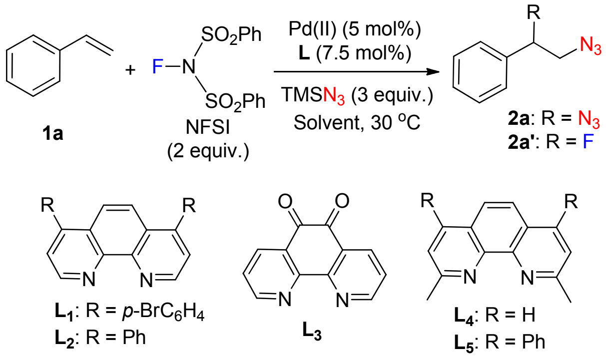
General procedure for palladium-catalyzed diazidation of internal alkenes

In a dried glass tube, $Pd(OTFA)_2$ (5.3 mg, 0.015 mmol), $\mathbf{L}_1$ (10.8 mg, 0.023 mmol), NFSI (365.0 mg, 1.0 mmol) were dissolved in DMF or 1,4-dioxane (0.8 mL), and then internal alkenes **3** (0.5 mmol), $TMSN_3$ (1.5 mmol) and water (0.63 mL) were added. The reaction mixture was stirred at room temperature for 1—3 h. After the reaction was completed, the mixture proceeded with the same workup to afford pure products.

Results and Discussion

Initial studies commenced from the reaction of styrene **1a**, $TMSN_3$ and NFSI in the presence of $PdCl_2$ and 2,2'-bipyridine (bpy), which indeed gave the vicinal diazidation product **2a** in 30% yield, companied by 10% azidofluorination product **2a'** (Table 1, Entry 1). With the screening on the bidentate nitrogen ligands, $\mathbf{L}_1$ was proven to be the best ligand to afford **2a** in 50% yield, companied with the side azidofluorination product **2a'** in 17% yield (Entries 2—8). In contrast, other phenanthroline type ligands gave even worse results, while pyridine was inactive. Further palladium catalyst screening showed that $Pd(OTFA)_2$ exhibited better reactivity than other palladium catalyst to give the desired product **2a** (Entries 9—11). Solvent investigation revealed that DCE and toluene were less efficient than dioxane to give the mixture of **2a** and **2a'** in lower yields (Entries 12, 13), and THF showed the similar result as dioxane (Entry 14). To our delight, when the solvent was switched to DMF, the yield of **2a** increased to 92% with 3 mol% catalyst loading, and the side azidofluorination was completely inhibited (Entry 15). Controlling experiment indicated that no reaction occurred in the absence of palladium catalyst or ligand (Entries 16, 17).

Table 1 Optimization of the reaction conditions[a]

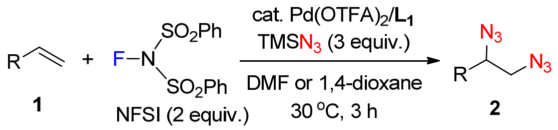


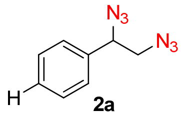
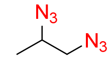
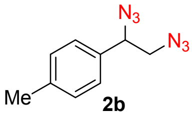
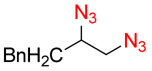
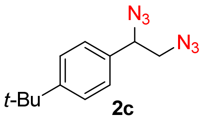
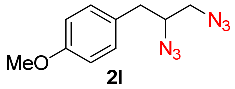
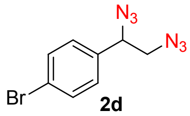
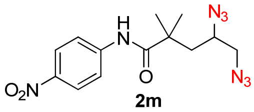
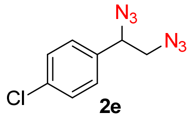
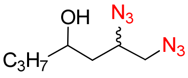
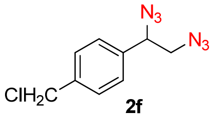
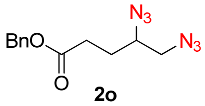
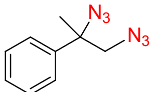
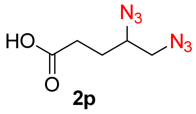
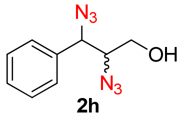
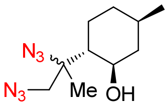
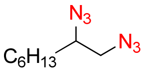
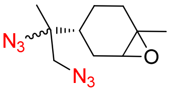
Entry	Pd(II)	Ligand	Solvent	Yield[b]/%	
				2a	**2a'**
1	$PdCl_2$	bpy	1,4-Dioxane	30	10
2	$PdCl_2$	Phen	1,4-Dioxane	13	10
3	$PdCl_2$	$\mathbf{L}_1$	1,4-Dioxane	50	17
4	$PdCl_2$	$\mathbf{L}_2$	1,4-Dioxane	8	30
5	$PdCl_2$	$\mathbf{L}_3$	1,4-Dioxane	30	11
6	$PdCl_2$	$\mathbf{L}_4$	1,4-Dioxane	31	5
7	$PdCl_2$	$\mathbf{L}_5$	1,4-Dioxane	0	0
8[c]	$PdCl_2$	py	1,4-Dioxane	0	0
9	$Pd(OAc)_2$	$\mathbf{L}_1$	1,4-Dioxane	60	0
10	$Pd(OTFA)_2$	$\mathbf{L}_1$	1,4-Dioxane	70	10
11	$Pd(PPh_3)_2Cl_2$	$\mathbf{L}_1$	1,4-Dioxane	50	0
12	$Pd(OTFA)_2$	$\mathbf{L}_1$	DCE	33	15
13	$Pd(OTFA)_2$	$\mathbf{L}_1$	Toluene	38	20
14	$Pd(OTFA)_2$	$\mathbf{L}_1$	THF	65	0
15[d]	$Pd(OTFA)_2$	$\mathbf{L}_1$	DMF	92	0
16	$PdCl_2$	None	1,4-Dioxane	0	0
17	None	$\mathbf{L}_1$	1,4-Dioxane	0	0

[a] Reaction conditions: **1a** (0.2 mmol), Pd catalyst (5 mol%), $\mathbf{L}_1$ (7.5 mol%), NFSI (2 equiv.) and $TMSN_3$ (3 equiv.) in solvent (0.5 mL) at 30 ℃. [b] ^1H NMR yield with CF_3-DMA as internal standard. [c] 15 mol% pyridine. [d] $Pd(OTFA)_2$ (3 mol%), $\mathbf{L}_1$ (4.5 mol%).

With the optimized reaction condition in hands, substrate scope was further investigated. Styrenes with different substituents on *para* carbon position were proven to be good substrates to give corresponding vicinal alkyl diazides **2b**—**2f** in good to excellent yields (60%—83%). For the 1,1-disubstituted styrene, the reaction of *α*-methyl styrene proceeded smoothly to give product **2g** in 68% yield. Furtermore, the internal styrene *E*-cinnamyl alcohol was also compatible to the reaction condition, and the related alkyl diazide **2h** was provided in 69% yield, but with poor diastereoselectivity (1∶1 *dr* ratio). In addition to the activated styrene substrates, unactivated alkenes were surveyed. In this case, addition of *p*-nitrobenzoic acid as additive and increasing catalysis loading (from 3 mol% to 5 mol%) were beneficial to reach satisfying yields. For instance, the corresponding alkyl diazides **2i**—**2p** were obtained in

Table 2 Substrates scope of terminal alkenes[a,b]



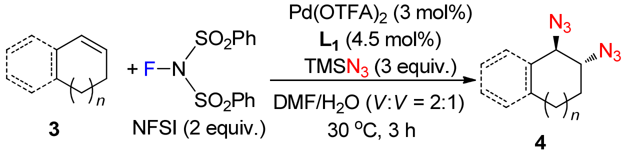
2	Yield/%	**2**	Yield/%
 **2a**	93	 **2j**	65
 **2b**	80	 **2k**	69
 **2c**	83	 **2l**	73[c]
 **2d**	81	 **2m**	75
 **2e**	80	 **2n**	50 (1∶1)[d]
 **2f**	60	 **2o**	72
 **2g**	68	 **2p**	70
 **2h**	69 (1∶1)[d]	 **2q**	65 (1∶1)[d]
 **2i**	85	 **2r**	35 (1∶1)[d]

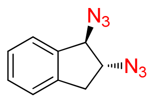
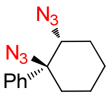
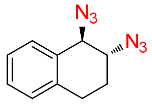
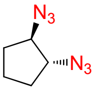
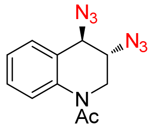
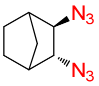
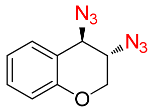
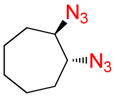
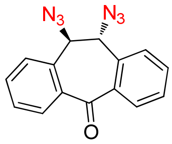
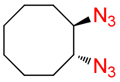
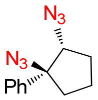
[a] Reaction conditions: for styrenes, Pd(OTFA)$_2$ (3 mol%), **L$_1$** (4.5 mol%), NFSI (2.0 equiv.), TMSN$_3$ (3.0 equiv.), **1** (0.5 mmol) in DMF (1.3 mL) at 30 ℃ for 3 h; for unactivated alkenes, Pd(OTFA)$_2$ (5 mol%), **L$_1$** (7.5 mol%), NFSI (2.0 equiv), TMSN$_3$ (3.0 equiv.), **1** (0.5 mmol) and *p*-NO$_2$-PhCOOH (3 equiv.) in 1,4-dioxane (1.3 mL) at 30 ℃ for 3 h. [b] Isolated yield. [c] 1,2,3-Triazide product was isolated in 18% yield. [d] *dr* ratio was determined by crude ^{1}H NMR analysis.

moderate to good yields (50%—85%). Notably, good functional group tolerance was observed in the reaction condition. For example, free amide, alcohol and carboxylic acid were compatible to give the desired products in good yields. The natural compounds, isopulegol **1q** and limonene 1,2-epoxide **1r**, were applied, and the reactions provided the desired products **2q** and **2r** in 65% and 35% yield respectively, but still with poor diastereoselectivity (1∶1 *dr*).

Finally, we turned our attention to the cyclic alkenes. As shown in Table 3, 1*H*-indene **3a** was treated under standard conditions to give **4a** in 70% yield with 2∶1 *dr* (see SI). However, the diastereoselectivity was dramatically improved to 10∶1 by using water as a

Table 3 Substrates scope of cyclic alkenes[a,b]

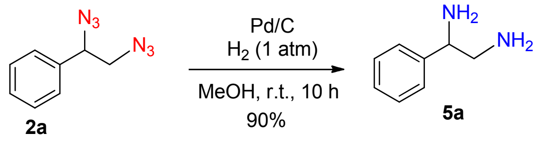


4	Yield/%	**4**	Yield/%
 **4a**	60 (10∶1)	 **4g**	73 (6∶1)
 **4b**	70 (8∶1)	 **4h**	69 (6∶1)
 **4c**	53[c]	 **4i**	67 (5∶1)
 **4d**	63[c]	 **4j**	76 (3∶1)
 **4e**	87 (3∶1)	 **4k**	89 (3∶1)
 **4f**	60[c]		

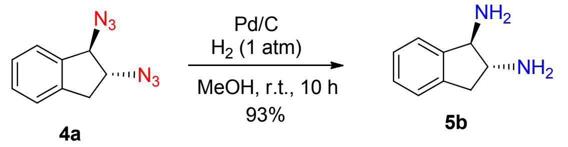
[a] Reaction conditions: Pd(OTFA)$_2$ (3 mol%), **L$_1$** (4.5 mol%), NFSI (2.0 equiv.), TMSN$_3$ (3.0 equiv.), **3** (0.5 mmol) in DMF/H$_2$O (2 mL, 2∶1) at 30 ℃ for 3 h. [b] Isolated yield, *dr* of *trans* and *cis* in parentheses was determined by crude ^{1}H NMR analysis. [c] Single isomer.

co-solvent, but the details of water effect on this transformation is unclear at the moment.[8] Similar result was observed in the case of 1,2-dihydronaphthalene **3b**. Notably, the reactions of 1,2-dihydroquinoline **3c** and 2*H*-chromene **3d** afforded *trans*-products **4c** and **4d** as sole isomers in moderate yields. And symmetric alkene 5*H*-dibenzo[*a*,*d*][7]annulen-5-one (**3e**) was also a suitable substrate to give **4e** in 87% yield, but with slightly poor *dr* ratio (3 ∶ 1). Interestingly, the reaction of *α*-phenyl cyclopentene **3f** presented excellent diastereoselectivity to afford a single isomer **4f** in 60% yield. While the reaction of *α*-phenyl cyclohexene delivered moderate *dr* ratio (6 ∶ 1) to give **4g** in 73% yield. Unactivated cyclic alkenes, ranged from five to eight membered rings, were also compatible to give **4h**—**4k** in good yields with moderate diastereoselectivities (3—6 ∶ 1).

Furthermore, the utility of vicinal alkyl diazides was investigated. As shown in Eqs. 1, 2, the alkyl diazides compounds **2a** and **4a** could be easily converted to the corresponding 1,2-diamines **5a** and **5b** through hydrogenation reaction by using Pd/C catalyst in excellent yields.



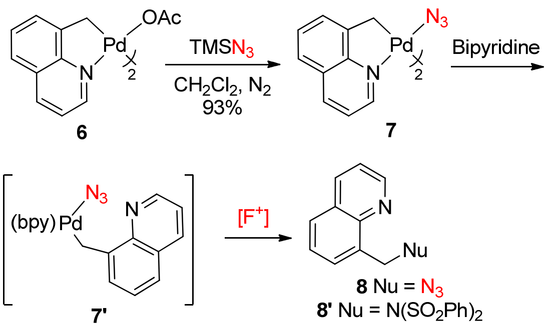
(1)



(2)

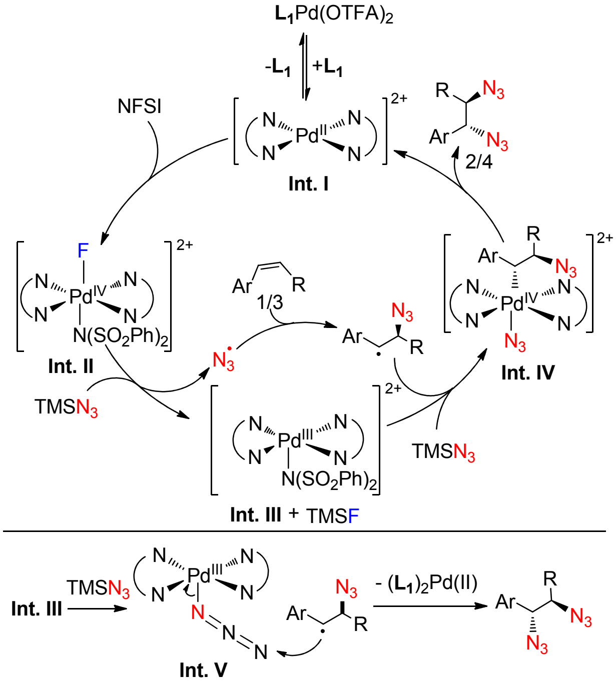
As similar to our previously reported sulfonylfluorination of styrenes,[7] the reductive elimination of Pd(IV) species was proposed to form the second C—N_3 bond. However, Canty *et al.*[9] disclosed that the reductive elimination of $\mathbf{L}Pd^{IV}Me_2(N_3)$ only gave Pd(II)-N_3 and ethane. Later, Grushin *et al.*[10,11] reported that the reductive elimination of Pd(II)-N_3 complexes only occurred in the case of steric bulky ligand, such as Xantphos. In order to give insight on this point, an alkyl-Pd-N_3 complex **7** was synthesized through ligand exchange, and employed to survey the azidation reaction. As shown in Scheme 2, after addition of bipyridine to an alkyl-Pd-N_3 dimer complex **7**, the formed monomer **7'** was treated by various of F^+ reagent. When NFSI was used as oxidant, the reaction provided major azidation product **8**, companied with amidation product **8'** with a 4.5 ∶ 1 ratio. However, the amidation reaction could be inhibited by using fluoropyridinium and Selectfluor. In contrast, no reaction occurred in the absence of oxidant. These results indicated the feasibility of $C(sp)^3$-N_3 reductive elimination from Pd(IV) species, which is unsuccessful in former studies.

Scheme 3



oxidant	yield of **8** (**8'**)/%
—	0 (0)
NFSI	36 (8)
2,6-ClPy-F	40 (0)
Selectfouor	80 (0)

Scheme 3 Proposed mechanism



Based on above observations, we proposed a mechanism shown in Scheme 3. First, oxidation of cationic $[(\mathbf{L_1})_2Pd]^{2+}$ (**Int.I**) by NFSI provides $[(\mathbf{L_1})_2Pd(F)N(SO_2Ph)_2]^{2+}$ (**Int.II**), which could oxidize $TMSN_3$ via a SET process to generate azido radical and $(\mathbf{L_1})_2Pd^{III}$ species **Int.III**. The former undergoes quick addition to alkenes to give an carbon radical, which is probably trapped by Pd(III) species **Int.II** to yield a high valent Pd(IV) species **Int.IV.** The subsequent ligand exchange and reductive elimination afford vicinal diazides product (top).[12] Alternatively, **int.III** might react with $TMSN_3$ to give Pd^{III}-N_3 complex **int.V**, which is then attacked by carbon radical at external nitrogen atom to give product and release $(\mathbf{L_1})_2Pd(II)$ species (bottom). However, the direct coupling of carbon radical intermediate with azido radical to give product can not be excluded at this moment.

Conclusions

In conclusion, we have developed a palladium-catalyzed oxidative vicinal diazidation of alkenes, in which $TMSN_3$ was used as the azide source and NFSI was used as oixdant. Both styrenes and unactivate alkenes could be transferred to corresponding vicinal diazides with this method. And *trans* diazides were obtained as major products from cyclic alkenes with moderate to good diastereoselectivities. This reaction afforded an efficient way for the synthesis of useful 1,2-diamines after hydrogenation. Further mechanism study and improvement on the stereoselectivity are in progress.

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(Zhao, C.)