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New Reactivity of Oxaziridine: Pd(II)-Catalyzed Aromatic C−H Ethoxycarbonylation via C−C Bond Cleavage

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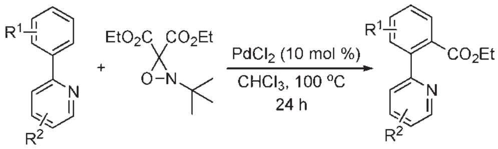
ABSTRACT



A novel Pd(II)-catalyzed aromatic C−H ethoxycarbonylation with oxaziridine involving C−C bond cleavage is described. Various aromatic 2-phenylpyridines and related compounds as well as aryl ureas can be effectively ethoxycarbonylated. A catalytic cycle involving Pd(II) and Pd(IV) is proposed.

Three-membered ring compounds containing two heteroatoms are highly versatile oxidation reagents.[1−3] As part of our general interest in the reactivity and selectivity of dioxirane[1g] and its nitrogen analogues, we have explored various metal-catalyzed transformations of diaziridinone and related compounds, including Pd(0)- and Cu(I)-catalyzed diamination of dienes,[4] Pd(0)-catalyzed allylic and homoallylic C−H amination of terminal olefins,[5] and Cu(I)-catalyzed C−H α-amination of esters[6] using di-

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(1) For general leading reviews on dioxiranes, see: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (d) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (e) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (f) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, 219. (g) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (h) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (i) Wang, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958. (j) Adam, W.; Zhao, C.-G.; Jakka, K. *Org. Rect.* **2007**, *69*, 1.

(2) For leading reviews on oxaziridines see: (a) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703. (b) Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327. (c) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919. (d) Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269.

(3) For a leading review on diaziridines and related compounds, see: Heine, H. W. In *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1983; p 547.

(4) (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Yuan, W.; Du, H.; Zhao, B.; Shi, Y. *Org. Lett.* **2007**, *9*, 2589. (c) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688. (d) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523. (e) Zhao, B.; Peng, X.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 11009.

(5) (a) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. (c) Wang, B.; Du, H.; Shi, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8224.

(6) Zhao, B.; Du, H.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220.

(7) For leading reviews on Pd-catalyzed C−H activations, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Hartwig, J. F. *Nature* **2008**, *455*, 314. (e) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (h) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412. (i) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (j) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824. (k) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(8) For recent examples of C-H functionalization of 2-phenylpyridines and related compounds, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *129*, 2300. (b) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (c) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (d) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (e) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466. (f) Jin, W.; Yu, Z.; He, W.; Ye, W.; Xiao, W.-J. *Org. Lett.* **2009**, *11*, 1317. (g) Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009**, *11*, 3120. (h) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (i) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249.

(9) For recent examples of synthetic transformations with oxazidines, see: (a) Brodsky, B. H.; Du Bois, J. *J. Am. Chem. Soc.* **2005**, *127*, 15391. (b) Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713. (c) Armstrong, A.; Challinor, L.; Moir, J. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5369. (d) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 1866. (e) Allen, C. P.; Benkovics, T.; Turek, A. K.; Yoon, T. R. *J. Am. Chem. Soc.* **2009**, *131*, 12560. (f) Partridge, K. M.; Guzei, I. A.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 930. (g) Benkovics, T.; Guzei, I. A.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9153.

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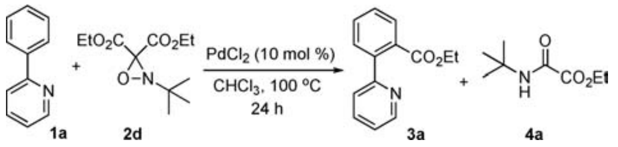
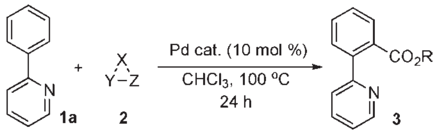
tert-butyldiaziridinone or *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide as nitrogen source. During our ongoing studies on the reactivity of diaziridine and its analogues, we have found that aromatics such as 2-phenylpyridines and related compounds can be ethoxycarbonylated with certain oxaziridines via a process involving C–C bond cleavage in the presence of Pd catalyst (Scheme 1).[7–10] The aromatic C–H alkoxycarbonylation[11–16] process described herein introduces a novel reactivity of oxaziridines.

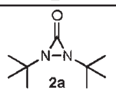
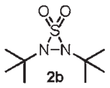
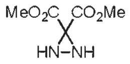
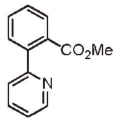
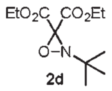
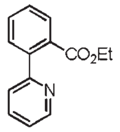
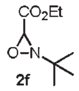
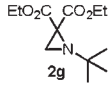
Scheme 1



Reactivity studies of three-membered heterocyclic compounds were carried out with 2-phenylpyridine (**1a**) as test substrate and with various Pd-sources as catalysts. As shown in Table 1 (entries 1–4), no reaction occurred when 2-phenylpyridine (**1a**) was treated with di-*tert*-butyldiaziridinone (**2a**) or *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide (**2b**) in the presence of 10 mol % $PdCl_2$ or 5 mol % $Pd_2(dba)_3$ in $CHCl_3$ at 100 °C for 24 h. However, a small amount of methoxycarbonylation product **3aa** was isolated when diaziridine **2c** was used with 10 mol % $PdCl_2$ (Table 1, entry 5). Interestingly, ethoxycarbonylation product **3a** was formed in 94% conversion along with amide **4a** when oxaziridine **2d** was used (Table 1, entry 7). Good conversions were also obtained with other Pd catalysts (Table 1, entries 8–12). Oxaziridines **2e** and **2f** were also found to be capable of ethoxycarbonylating 2-phenylpyridine (**1a**), but aziridine **2g** was ineffective for the reaction (Table 1, entries 13–18).

Table 1. Reactivity Studies with Various Three-membered Heterocyclic Compounds[a]



entry	2	catalyst	product	conv (%)[b]
1	 2a	$PdCl_2$	NR	-
2		$Pd_2(dba)_3$	NR	-
3	 2b	$PdCl_2$	NR	-
4		$Pd_2(dba)_3$	NR	-
5	 2c	$PdCl_2$	 3aa	20
6		$Pd_2(dba)_3$		-
7	 2d	$PdCl_2$	 3a	94
8		$Pd(CH_3CN)_2Cl_2$		85
9		$Pd(TFA)_2$		89
10		$Pd(OAc)_2$		81
11		$Pd(PPh_3)_4$		64
12		$Pd_2(dba)_3$		74
13	 2e	$PdCl_2$	3a	37
14		$Pd_2(dba)_3$	3a	32
15	 2f	$PdCl_2$	3a	80
16		$Pd_2(dba)_3$	3a	78
17	 2g	$PdCl_2$	NR	-
18		$Pd_2(dba)_3$	NR	-

[a] All reactions were carried out with 2-phenylpyridine (**1a**) (0.2 mmol), **2** (0.4 mmol), Pd catalyst (0.02 mmol) in $CHCl_3$ (0.5 mL) at 100 °C for 24 h. [b] The conversion was based on 2-phenylpyridine (**1a**) and determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture.

The $PdCl_2$-catalyzed ethoxycarbonylation with oxaziridine **2d** can be extended to a variety of substituted 2-phenylpyridines. As shown in Table 2, various substituents including electron-donating and electron-withdrawing groups are tolerable under the reaction conditions. Somewhat lower yields obtained for entries 2, 10, and 11 could be attributed to the steric effect of the *o*-methyl substituent. Pyrimidine and benzo[*h*]quinoline

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(10) For recent reviews on C–C activations, see: (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) Horino, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2144. (c) Jun, C.-H.; Park, J.-W. *Top. Organomet. Chem.* **2007**, *24*, 117. (d) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (e) Nájera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (f) Winter, C.; Krause, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 2460. (g) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100.

(11) For Pd(II)-catalyzed alkoxycarbonylation with CO/ROH and oxidant [benzoquinone or $Cu(OAc)_2$], see: (a) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416. (b) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830. (c) Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, *39*, 10442.

(12) For Pd(II)-catalyzed carboxylation with CO and oxidant ($K_2S_2O_8$, O_2, or Ag_2CO_3), see: (a) Lu, W.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1999**, *580*, 290. (b) Ohashi, S.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2005**, 486. (c) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082.

(13) For Pd(II)-catalyzed C-H alkoxycarbonylation with diethylazodicarboxylate (DEAD) and oxidant (oxone or $K_2S_2O_8$), see: Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304.

(14) For Pd(II)-catalyzed aromatic C–H carbonylation with CO and oxidant [$Cu(OAc)_2$] to form benzolactams, see: Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342.

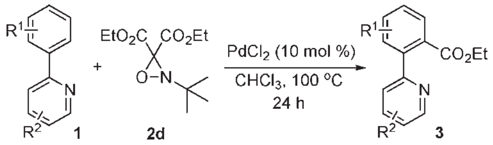
(15) For Ru(II)-catalyzed C–H alkoxycarbonylation with $ClCO_2R$, see: Kochi, T.; Urano, S.; Seki, H.; Mizushima, E.; Sato, M.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 2792.

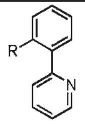
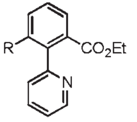
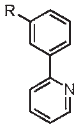
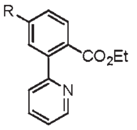
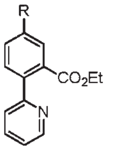
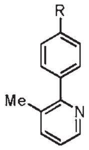
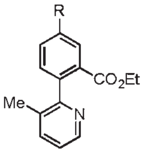
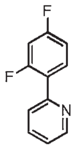
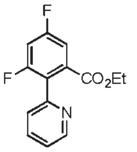
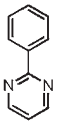
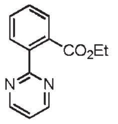
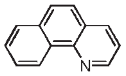
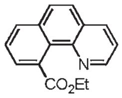
(16) For Rh(I)-catalyzed C–H alkoxycarbonylation with CO/ROH, and oxone, see: Guan, Z.-H.; Ren, Z.-H.; Spinella, S. M.; Yu, S.; Liang, Y.-M.; Zhang, X. *J. Am. Chem. Soc.* **2009**, *131*, 729.

(17) For recent examples of C–H functionalization of aryl ureas, see: (a) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (b) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874. (c) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781. (d) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978. (e) Wei, Y.; Ding, H.; Lin, S.; Liang, F. *Org. Lett.* **2011**, *13*, 1674.

were also found to be effective substrates (Table 2, entries 13 and 14).

Table 2. $PdCl_2$-catalyzed C−H Ethoxycarbonylation of Aryl Pyridine Derivatives with **2d**[a]

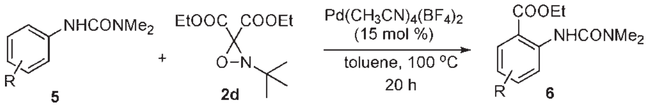


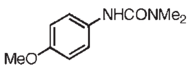
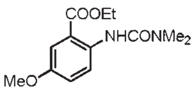
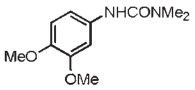
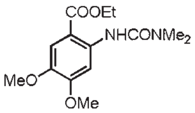
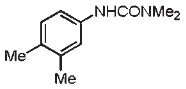
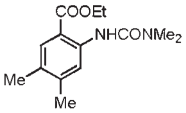
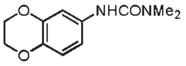
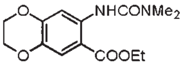
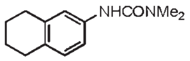
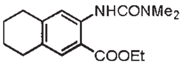
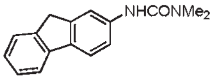
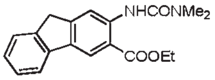
entry	substrate 1		product 3	yield (%)[b]
1 2		**1a**, R = H **1b**, R = Me		88 52
3 4		**1c**, R = Me **1d**, R = Cl		66 65
5 6 7 8 9		**1e**, R = OMe **1f**, R = Me **1g**, R = Cl **1h**, R = CHO **1i**, R = CF_3		70 68 57 57 54
10 11		**1j**, R = H **1k**, R = OMe		50 55
12		**1l**		72
13		**1m**		66
14		**1n**		88

[a] All reactions were carried out with substrate **1** (0.2 mmol), **2d** (0.4 mmol), $PdCl_2$ (0.02 mmol) in $CHCl_3$ (0.5 mL) at 100 °C for 24 h. [b] Isolated yield based on substrate **1**.

Besides aryl pyridines, the ethoxycarbonylation can also be applied to aryl ureas **5** using $Pd(CH_3CN)_4(BF_4)_2$ as catalyst.[17] As shown in Table 3, various substituted aryl ureas were ethoxycarbonylated at the positions ortho to the ureas to give anthranilates **6**, and essentially only one isomer was isolated.

Table 3. $Pd(CH_3CN)_4(BF_4)_2$-catalyzed C−H Ethoxycarbonylation of Aryl Urea Derivatives with **2d**[a]

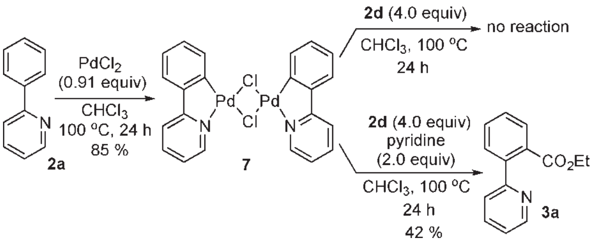


entry	substrate 5	product 6	yield (%)[b]
1	 **5a**		53
2	 **5b**		57
3	 **5c**		52
4	 **5d**		51
5	 **5e**		52
6	 **5f**		46

[a] All reactions were carried out with substrate **5** (0.2 mmol), **2d** (0.6 mmol), $Pd(CH_3CN)_4(BF_4)_2$ (0.03 mmol) in toluene (0.8 mL) at 100 °C for 20 h. [b] Isolated yield based on substrate **5**.

When 2-phenylpyridine (**1a**) was treated with $PdCl_2$ in $CHCl_3$ at 100 °C for 24 h, a yellow solid likely to be palladacycle **7** was obtained in 85% yield (Scheme 2).[18,19]

Scheme 2



Compound **7** was insoluble in $CHCl_3$, and no product was obtained when it was treated with oxaziridine **2d** at

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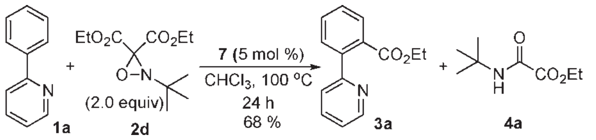
(18) For leading reviews on palladacycles, see: (a) Ryabov, A. D. *Synthesis* **1985**, 233. (b) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527.

(19) For leading references on the formation of dimeric palladacycles from 2-phenylpyridine and M_2PdCl_4 or $Pd(OAc)_2$, see: (a) Craig, C. A.; Watts, R. J. *Inorg. Chem.* **1989**, *28*, 309. (b) Constable, E. C.; Thompson, A. M. W. C.; Leese, T. A.; Reese, D. G. F.; Tocher, D. A. *Inorg. Chim. Acta* **1991**, *182*, 93. (c) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974.

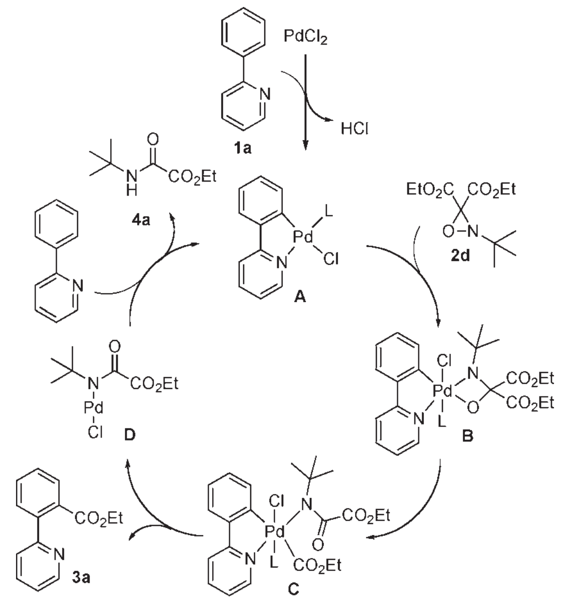
100 °C for 24 h (Scheme 2). However, compound **7** dissolved immediately in $CHCl_3$ when 2.0 equiv of pyridine was added. When the resulting solution was treated with oxaziridine **2d** at 100 °C for 24 h, ethoxycarbonylation product **3a** was isolated in 42% yield (Scheme 2). It is likely that the pyridine first converts dimeric **7** into a monomeric Pd species, which then reacts with oxaziridine **2d** to form the ethoxycabonylation product. Palladacycle **7** was also shown to be catalytically active. Compound **3a** was isolated in 68% yield when 2-phenylpyridine (**1a**) was treated with oxaziridine **2d** in the presence of 5 mol % **7** (Scheme 3). In this case, in addition to being a substrate, 2-phenylpyridine (**1a**) could also act as a ligand to break the dimeric structure of **7** like pyridine did in the earlier case.[20]

Scheme 3



On the basis of the above results, a tentative catalytic pathway involving Pd(II) and Pd(IV) is shown in Scheme 4. $PdCl_2$ reacts with 2-phenylpyridine to generate Pd(II) intermediate **A** via C–H activation.[7,21,22] The Pd(II) then inserts into the N–O bond of oxaziridine **2d** to form Pd(IV) species **B**, which rearranges to Pd(IV) species **C** by a shift of CO_2Et from the carbon to the Pd via a C–C bond cleavage process. The reductive elimination of compound **C** forms ethoxycarbonylation product **3a** and Pd(II) species **D**. Pd(II) species **A** is then regenerated from **D** along with the formation of amide **4a**. At this moment, other alternative pathways cannot be excluded. Better understanding of the reaction mechanism awaits further study.

Scheme 4. Proposed Catalytic Cycle for the Ethoxycarbonylation



In summary, a novel Pd(II)-catalyzed aromatic C–H ethoxycarbonylation with oxaziridine has been observed. Various 2-phenylpyridines and related compounds as well as aryl ureas can be effectively ethoxycarbonylated. The reaction process likely proceeds via a Pd(II)/Pd(IV) catalytic cycle and involves a C–C bond cleavage of oxaziridines.[2d] Oxaziridines act as a CO_2Et group donor as well as an oxidant, which illustrates a new type of reactivity for this class of three-membered heterocyclic compounds. Further mechanistic studies and development of other reaction processes with oxaziridines and related compounds are currently underway.

Acknowledgment. We are grateful to the financial support from the ACS Arthur C. Cope Fund.

Supporting Information Available. Experimental procedures and characterization data along with ^1H NMR and ^{13}C NMR spectra of **2c**–**g**, **3**, **4** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] (a) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc., Chem. Commun.* **1978**, 1061. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234.

[21] (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (b) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.

[22] Addition of bases such as pyridine, NEt_3 or Na_2CO_3 lowered the reaction yield.