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Palladium-Catalyzed Oxidative Activation of Arylcyclopropanes

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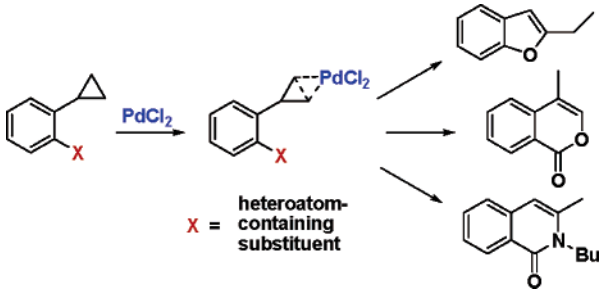
ABSTRACT



Palladium chloride-catalyzed intramolecular activation of electroneutral cyclopropane derivatives results in cleavage of the cyclopropane ring followed by formation of heterocyclic derivatives. Phenols, carboxylic acids, and amide groups were considered as substituents ortho to the cyclopropane ring in this catalytic activation chemistry. The regioselectivity observed in the case of amide-containing substrates was different from that of carboxylic acid-containing substrates, ruling out simple cyclopropane isomerization followed by a Wacker oxidation as the mechanistic pathway.

A cyclopropane ring can be found within the structures of natural products such as curacin A, ambruticin, and halicholactone, to name a few.[1] Methods for the cyclopropane ring construction have been thoroughly investigated.[2] Although synthetic applications of the "donor−acceptor" cyclopropanes are well precedented,[3] the utility of "electroneutral" cyclopropanes in synthesis is far less established.[4] Herein, we report a palladium chloride-catalyzed intramolecular activation of electroneutral cyclopropane derivatives.

In terms of electronic structure, cyclopropanes are closer to olefins than to other cycloalkanes. The orbitals of C−H bonds in the simplest member of this class of compounds, C_3H_6, have approximately 33% s-character, whereas those of C−C bonds have 17% s-character.[5] The electron-rich nature of electroneutral cyclopropane rings manifests itself in reactions with strong acids. Corner- and edge-protonated cyclopropyl species have been postulated as intermediates.[6] Attempts to activate C−C bonds in substituted cyclopropanes with palladium catalysts have been made.[7] The late transition metals react with cyclopropanes when placed in their vicinity by way of initial addition to the nearby olefin.[8] The ring expansion of highly reactive methylenecyclopropanes can

(1) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.

(2) *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 1987; Vol. 1.

(3) (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.

(4) In this paper, the term "electroneutral" refers to the cyclopropanes that do not have carbon- or heteroatom-containing electron-withdrawing and/or electron-donating substituents.

(5) Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1967**, *89*, 5962.

(6) (a) Bodor, N.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1971**, *93*, 6685. (b) McKinney, M. A.; Smith, S. H.; Hempelman, S.; Gearen, M. M.; Pearson, L. *Tetrahedron Lett.* **1971**, *39*, 3657. (c) Lee, C. C.; Vassie, S.; Ko, E. C. F. *J. Am. Chem. Soc.* **1972**, *94*, 8931. (d) DePuy, C. H.; Andrist, A. H.; Fuenfschilling, P. C. *J. Am. Chem. Soc.* **1974**, *96*, 948. (e) DePuy, C. H.; Fuenfschilling, P. C.; Andrist, A. H.; Olson, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 6297. (f) Rood, I. D. C.; Klumpp, G. W. *Tetrahedron Lett.* **1983**, *24*, 4599. (g) Dewar, M. J. S.; Healy, E. F.; Ruiz, J. M. *J. Chem. Soc., Chem. Commun.* **1987**, *12*, 943. (h) Koch, W.; Liu, B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 3479. (i) Burritt, A.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1995**, *60*, 7670. (j) Frash, M. V.; Kazansky, V. B.; Rigby, A. M.; van Santen, R. A. *J. Phys. Chem.* **1998**, *102*, 2232.

(7) (a) Albelo, G.; Rettig, M. F. *J. Organomet. Chem.* **1972**, *42*, 183. (b) Albelo, G.; Wiger, G.; Rettig, M. F. *J. Am. Chem. Soc.* **1975**, *97*, 4510. (c) Rettig, M. F.; Wilcox, D. E.; Fleischer, R. S. *J. Organomet. Chem.* **1981**, *214*, 261. (d) Parra-Hake, M.; Rettig, M. F.; Wing, R. M.; Woolcock, J. C. *Organometallics* **1982**, *1*, 1478. (e) Ahmad, M. U.; Bäckvall, J.-E.; Nordberg, R. E.; Norin, T.; Strömberg, S. *J. Chem. Soc., Chem. Commun.* **1982**, *5*, 321. (f) Wilhelm, D.; Bäckvall, J.-E.; Nordberg, R. E.; Norin, T. *Organometallics* **1985**, *4*, 1296. (g) Parra-Hake, M.; Rettig, M. F.; Williams, J. L.; Wing, R. M. *Organometallics* **1986**, *5*, 1032.

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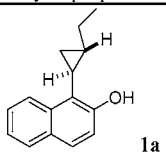
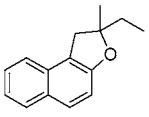
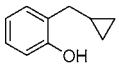
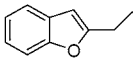
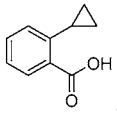
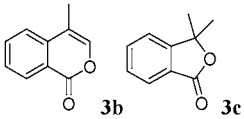
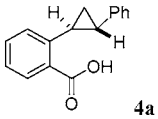
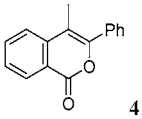
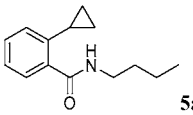
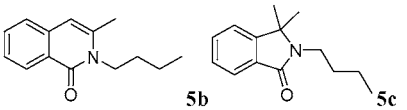
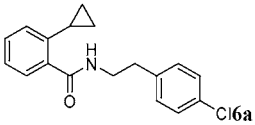
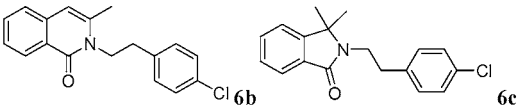
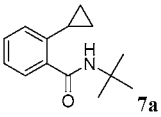
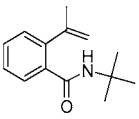
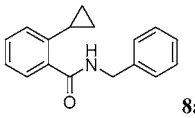
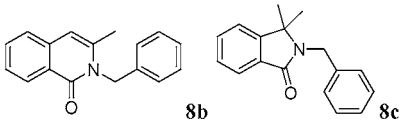
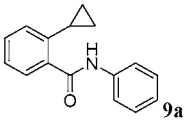
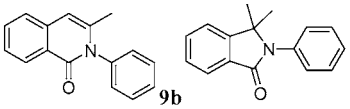
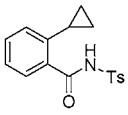
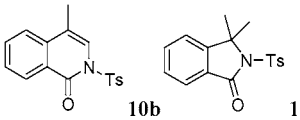
Table 1. Palladium-Catalyzed Oxidative Activation of Arylcyclopropanes[a]

entry	cyclopropane	product(s)[f]	yield (%)[b]
1[c,c]	 **1a**	 **1b**	64
2[d,c]	 **2a**	 **2b**	61
3[d]	 **3a**	 **3b** **3c**	76 (86:14)
4[d]	 **4a**	 **4b**	50
5	 **5a**	 **5b** **5c**	75 (87:13)
6	 **6a**	 **6b** **6c**	51 (84:16)
7[d]	 **7a**	 **7b**	43
8	 **8a**	 **8b** **8c**	50 (88:12)
9	 **9a**	 **9b** **9c**	68 (83:17)
10	 **10a**	 **10b** **10c**	60 (75:25)

[a] Unless otherwise noted, the reactions were carried out using 0.5 mmol of starting material, 10 mol % of $PdCl_2(MeCN)_2$ as catalyst, and 1.0 equiv of benzoquinone as oxidant in 5 mL of dioxane at 80 °C for 12 h. [b] Isolated yield with products ratio. [c] 30 mol % of $PdCl_2$ and 2.0 equiv of $CuCl_2$ were used. [d] 10 mol % of $PdCl_2$ and 2.0 equiv of $CuCl_2$ were used. [e] Reaction was carried out at 100 °C for 24 h. [f] The product(s) presented in the table were the only tractable organic compounds present in the reaction mixture upon completion.

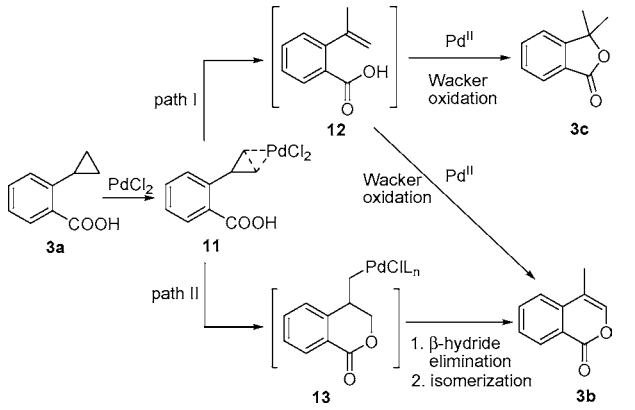
be triggered by aminopalladation of the double bond leading to α-palladated intermediates.[9] These reactions proceed by initial addition to the olefin rather than by direct activation of the cyclopropane ring by the metal ion.

With a series of starting materials prepared using standard cyclopropane chemistry,[10] we explored Pd^{II}-catalyzed activation of arylcyclopropanes bearing heteroatom substituents on the aromatic ring. Substituted carboxylic acids, amides, and phenols were subjected to the Pd^{II}-catalyzed oxidation conditions. We were pleased to observe that the cyclopropane ring activation took place, and the corresponding lactones, lactams, and ethers were formed in good yields (Table 1). Dioxane was found to be superior to DMF, toluene, THF, and DME as a solvent. Good yields were obtained with $PdCl_2$ or $PdCl_2(MeCN)_2$ catalysts. Lower activity was observed when $PdBr_2$, PdI_2, $Pd(OAc)_2$, or $Pd(TFA)_2$ was employed. Copper(II) chloride was a good choice of oxidant for phenols and acids; however, benzoquinone was superior to copper(II) chloride, $PhI(OAc)_2$, oxone, and O_2 as the oxidant in the case of amides. A number of additives such as pyridine,

(8) Larock, R. C.; Yum, E. K. *Tetrahedron* **1996**, *52*, 2743.
(9) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458.
(10) See Supporting Information.

Na_2HPO_4, Na_2CO_3, NaOAc, LiCl, and molecular sieves were evaluated, but all of them slowed down catalytic turnover.

Scheme 1. Proposed Mechanistic Pathway for Activation of Arylcyclopropyl Acids

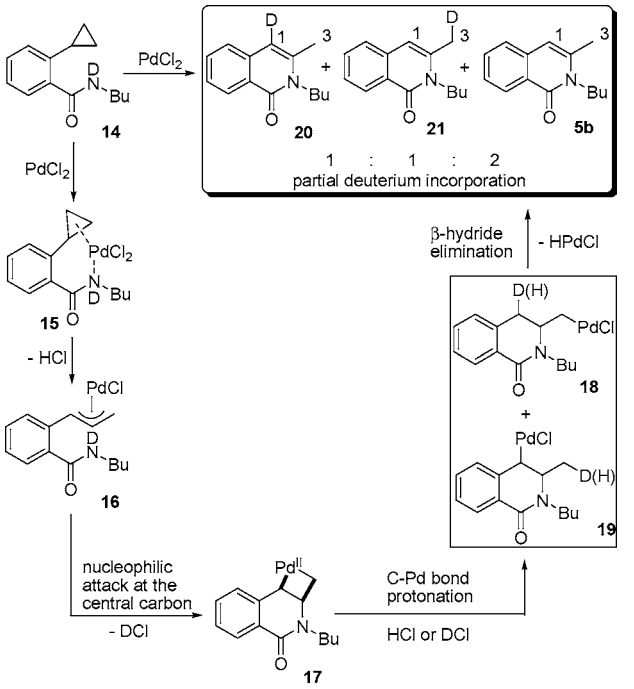


The α-methylstyrene derivative **12** (Scheme 1) was detected by ^{1}H NMR during the cyclization of **3a**, suggesting that a possible pathway in the case of carboxylic acid-containing substrates is Pd^{II}-catalyzed isomerization of the cyclopropane ring to the branched olefin followed by a Wacker oxidation (Scheme 1, path I). This pathway is also conceivable for the formation of phenol-containing arylcyclopropanes as well as for the formation of five-membered ring lactams (**5c**, **6c**, **8c**, **9c**, **10c**) in the case of amide-containing substrates. However, the formation of **3b** can also be explained by direct carboxypalladation followed by *β*-hydride elimination and subsequent olefin isomerization (Scheme 1, path II).[11a] The carboxypalladation is expected to occur upon initial coordination of Pd^{II} to the more electron-rich distal C−C bond of the arylcyclopropane.[11b]

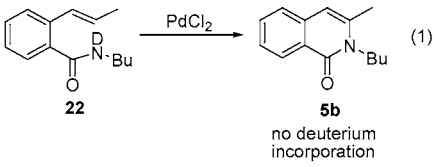
Interestingly, a different regioselectivity was observed in the formation of six-membered ring lactams (**5b**, **6b**, **8b**, **9b**) in the case of amides. In an attempt to clarify the underlying reasons, deuterium labeling experiments were carried out. Deuterium incorporation was detected in positions 1 and 3 of the six-membered ring product when deuterated amide **14** was subjected to the reaction conditions (Scheme 2).[12] This observation rules out simple cyclopropane−olefin isomerization followed by Wacker oxidation as the reaction pathway during Pd^{II}-promoted activation of amides. Furthermore, when deuterated amide **22** (eq 1) was subjected to the oxidation conditions, no deuterium incorporation was detected.

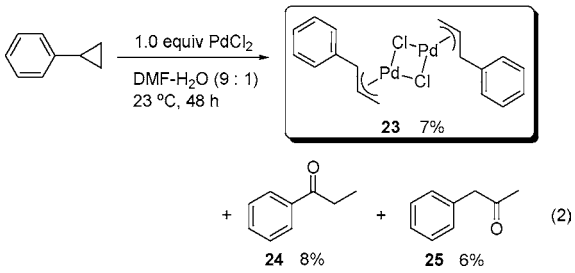
An attack at the central carbon of the *π*-allyl complex in the case of amides is consistent with our observations.[13,14] This can also be supported by isolation of the *π*-allyl complex

Scheme 2. Isotopic Labeling Experiments during Amide Activation



23 in the reaction of phenylcyclopropane and H_2O in the presence of $PdCl_2$ (eq 2). The acidic conditions would ensure





that palladium release by protonation of the C−Pd bond is the preferred reaction pathway. Accordingly, deuteration of the C−Pd bond would account for the incorporation of deuterium in positions 1 and 3.[14i]

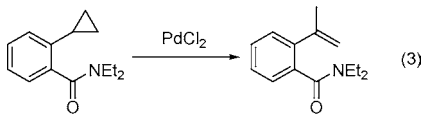
Although a precise mechanistic picture has not been fully established, it is clear that palladium−nitrogen coordination is the key factor that accounts for different selectivities observed during activation of acids and amides. The existence of this interaction has been confirmed by ^{1}H NMR through

(11) (a) For a recent example of *β*-alkoxy elimination in Wacker chemistry, see: Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778. (b) For a detailed molecular orbital discussion of phenylcyclopropane derivatives, see: Rademacher, P. *Chem. Rev.* **2003**, *103*, 933−975.

(12) No deuterium incorporation into the ring-opened product was detected in the case of the deuterated (COOD) derivative of acid **3a**.

(13) For the formation of *π*-allyl complexes during metal-promoted cyclopropane activation, see: (a) Tulip, T. H.; Ibers, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 9283. (b) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1984**, *106*, 7272.

the low-field shift of the amide proton when amide **5a** was mixed with $PdCl_2$ in dioxane-d_8,[10] whereas no coordination was observed in the acid case. The interaction between palladium and nitrogen is significantly suppressed in the case of *tert*-butyl amide **7a** and tertiary amide **26**, which convert to the branched olefins **7b** (Table 1, entry 7) and **27** (eq 3), respectively.



26 **27** (3)

In summary, electroneutral cyclopropane rings can be catalytically activated using $PdCl_2$ to give heterocyclic products. Interesting mechanistic trends have been uncovered, pointing toward dependence of the cyclopropane activation pathway on nearby substituents. Because of the wide accessibility of electroneutral cyclopropanes, including a range of chiral derivatives, one can anticipate benefits in synthetic sequences that would rely on oxidative elaboration of cyclopropanes. Just as palladium−olefin interactions have served as a rich source of new reactions, the palladium−cyclopropane union may also prove to be of utility. Investigations along these lines are currently underway.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council (NSERC), Canada Foundation for Innovation (CFI), Ontario Research and Development Challenge Fund (ORDCF), and Amgen for financial support.

Supporting Information Available: Experimental procedures and characterization data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062476E

(14) For nucleophilic attack on the central carbon of π-allyl palladium complexes, see: (a) Hegedus, L. S.; Darlington, W. H.; Russell, C. E. *J. Org. Chem.* **1980**, *45*, 5193. (b) Carfagna, C.; Galarini, R.; Musco, A. *J. Mol. Catal.* **1992**, *72*, 19. (c) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 234. (d) Formica, M.; Musco, A.; Pontellini, R. *J. Mol. Catal.* **1993**, *84*, 239. (e) Wilde, A.; Otte, A. R.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Commun.* **1993**, 615. (f) Castano, A. M.; Aranyos, A.; Szabó, K. J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2551. (g) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 100. (h) Aranyos, A.; Szabó, K. J.; Castano, A. M.; Bäckvall, J.-E. *Organometallics* **1997**, *16*, 1058. (i) Organ, M. G.; Miller, M.; Konstantinou, Z. *J. Am. Chem. Soc.* **1998**, *120*, 9283.