AFRL-OSR-VA-TR-2015-0035

Catalytic activation of nitrogen dioxide for selective synthesis

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01/15/2015
Final Report

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AF Office Of Scientific Research (AFOSR)/ RTE
Arlington, Virginia 22203
Air Force Materiel Command

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*
12-01-2015

2. REPORT TYPE
Final

3. DATES COVERED *(From - To)*
15 Aug 2011 - 14 Aug 2014

4. TITLE AND SUBTITLE
Catalytic activation of nitrogen dioxide for selective synthesis of nitroorganics

5a. CONTRACT NUMBER

5b. GRANT NUMBER
FA9550-11-1-0253

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Brown, Seth, N.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Notre Dame du Lac
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Notre Dame, IN 46556-5612
USA

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Air Force Office of Scientific Research
875 N. Randolph, Suite 325
Arlington, VA 22203

10. SPONSOR/MONITOR'S ACRONYM(S)
AFOSR

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Distribution A—Approved for Public Release

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The use of modern metal-catalyzed methods for production of nitroorganics has been impeded by the paucity of fundamental data on organometallic nitro compounds. Nitrotrimethylplatinum(IV) undergo reductive elimination reactions to form C-O and C-N bonds, at rates and by mechanisms similar to those previously observed for the corresponding acetate complexes. The reactions are unusually selective for C-O bond formation, forming more methyl nitrite than nitromethane. Arylpalladium(II) nitrites are formed as mixtures of O- and N-bonded compounds. Reductive elimination of the nitro group from these compounds is seldom observed, with C-P and C-C reductive elimination of ancillary phosphine ligands taking place preferentially, though traces of nitroarene are observed on thermolysis of (dppf)Pd(Ar)(NO2). Formation of Pd(IV) aryl compounds through oxidative addition of N2O4 has also been observed, though reductive elimination of the nitroarene has not. Nitrogen dioxide can be used as a source of the nitro group in reactions with arylboronic acids or their pinacol esters. In some cases, no catalyst is necessary, but in electron-rich systems catalysts (preferredly IrCl3(py)3) are needed to divert reactivity from electrophilic nitration to ipso nitro-deboronation.

15. SUBJECT TERMS

Catalysis; nitrogen dioxide; oxidative addition; reductive elimination; nitroarenes.

16. SECURITY CLASSIFICATION OF:

a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES
U	U	U	UU	6

19a. NAME OF RESPONSIBLE PERSON
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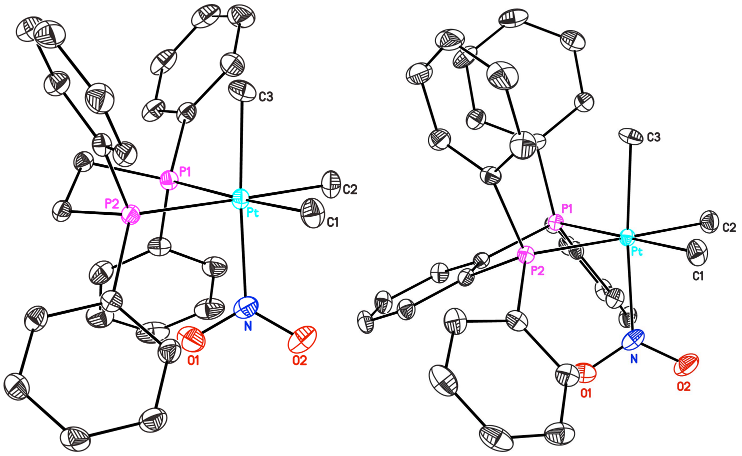
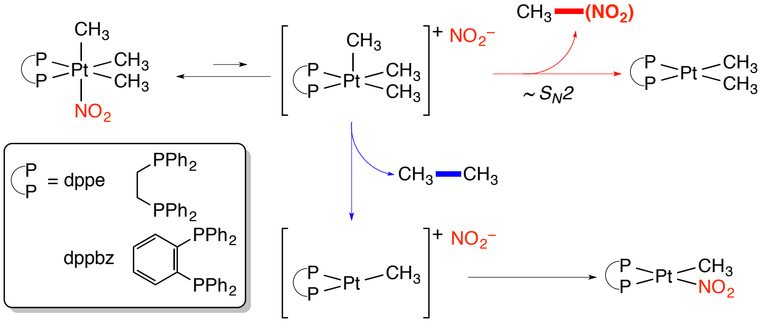
19b. TELEPHONE NUMBER *(include area code)*
574-631-4659

Reductive Elimination to Form Carbon-NO_2 Bonds. Contemporary methods in homogeneous metal-catalyzed organic synthesis rely heavily on reaction mechanisms that involve oxidative addition and reductive elimination reactions to break and form carbon-carbon and carbon-heteroatom bonds. Literature precedent regarding such reactions involving the NO_2 group is scant; not surprisingly, so are metal-catalyzed reactions that involve installing this group. We thus prepared (diphosphine)$Pt(CH_3)_3(NO_2)$ compounds (diphosphine = $Ph_2PCH_2CH_2PPh_2$ [dppe] and $Ph_2PC_6H_4PPh_2$ [dppbz]) to study their reactivity, allowing one to compare and contrast them to the behavior of known (diphosphine)$Pt(CH_3)_3X$ complexes.

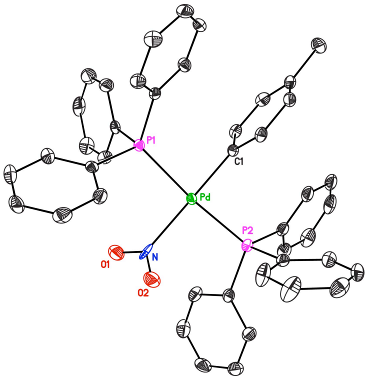


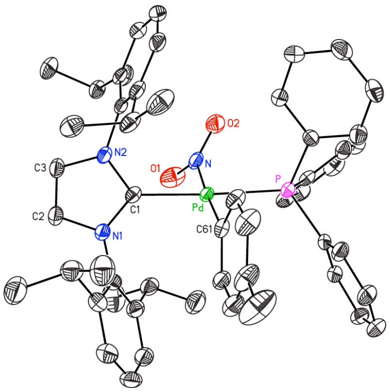
The compounds are structurally analogous to each other and to previously prepared trimethylplatinum compounds. Their thermolysis gives rise to both carbon-nitrite bond formation, with concomitant production of (diphosphine)$Pt(CH_3)_2$, and carbon-carbon bond formation with concomitant production of (diphosphine)$Pt(CH_3)(NO_2)$. Careful mechanistic studies indicate: (1) Reductive elimination is cleanly 1st-order in Pt, with rates of C–C reductive elimination increasing with increasing solvent polarity while rates of C–X reductive elimination are little affected by polarity. (2) C–C reductive elimination is strongly catalyzed by acids, with even traces of acids found adventitiously in chlorinated solvents diverting reactivity toward this pathway. (3) Reactions of the dppe and dppbz complexes proceed at very similar rates. These observations support an ionic mechanism for reductive elimination, where reaction is initiated by dissociation of nitrite ion, with C–X reductive elimination occuring by S_N2 attack of NO_2^- at a methyl group in the cationic Pt transient, while C–C reductive elimination takes place by coupling of methyl groups in this same intermediate.

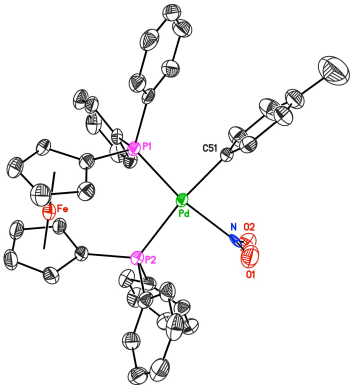


This mechanistic description is essentially identical to what has been found in other Pt(IV) methyl compounds. What is unique about nitrite is that it is an ambident nucleophile, and thus C–X reductive elimination forms mixtures of nitromethane by C–N bond formation and methyl nitrite by C–O bond formation. Organometallic reactions typically favor C–N over C–O bond formation, as do S_N2 reactions of, say, methyl iodide; in contrast, reductive elimination from platinum gives rise to high (and strongly solvent-dependent) selectivities in favor of C–O bond formation. In this case nitroso-organics are thus formed preferentially over nitroorganics.

Heteroatom-*aryl* bond formation often takes place quite differently from heteroatom-*alkyl* bond formation. This inspired us to prepare a variety of arylpalladium(II) nitrite complexes, the structures of some of which are shown below. In contrast to the Pt-NO_2 linkage, which appears to be exclusively bonded through nitrogen, Pd-NO_2 compounds generally exist as



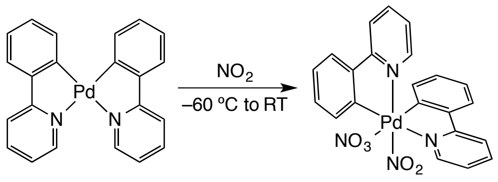


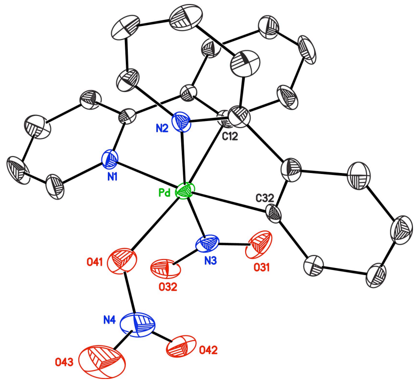


rapidly equilibrating mixtures of *N*-bonded nitro and *O*-bonded nitrito isomers, where the ratios and rates of interconversion can be determined by dynamic NMR measurements.

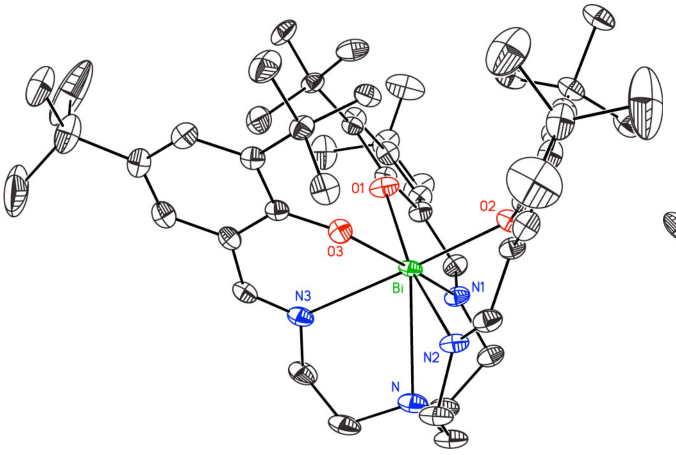
In most cases, thermolysis of these compounds does not produce nitroarenes. Heating $(Ph_3P)_2Pd(Ar)(NO_2)$ induces rapid scrambling between the Pd-*Ar* and the P*Ph*$_3$ groups, indicative of facile phosphorus-carbon oxidative addition/reductive elimination cycles. Prolonged thermolysis produces tetraarylphosphonium ions (again indicating preference for P–C reductive elimination) as well as some phosphine oxide. Thermolysis of $(Ph_3P)Pd(IPr)(C_6H_4CH_3)(NO_2)$ gives unusual C–C reductive elimination of the *N*-heterocyclic carbene to give the imidazolium salt $[CH_3C_6H_4\text{–}IPr]NO_2$. Only in the case of the bis(diphenylphosphino)ferrocene complex $[Fe(C_5H_4PPh_2)_2]Pd(Ar)(NO_2)$ were traces (5%) of nitroarene observed. These results suggest that aryl-nitro reductive elimination is not an intrinsically facile process and careful ligand optimization will be required in order to achieve catalytically useful systems.

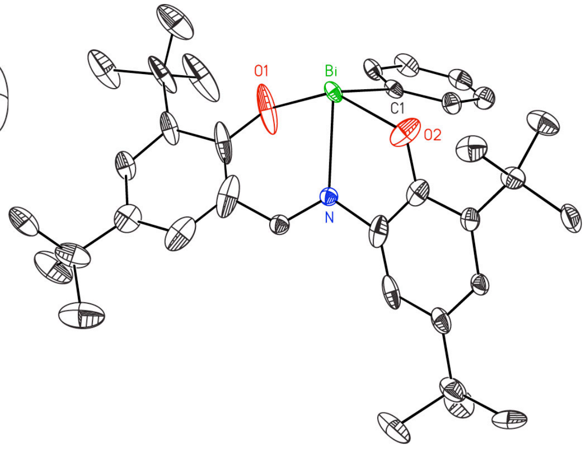
Oxidative Addition of N_2O_4 as a Step in C-H Activation. One of the most significant recent developments in organometallic catalysis is the successful functionalization of hydrocarbons under oxidative conditions by activation of C-H bonds (usually, though not always, directed by neighboring functional groups). Nitrogen dioxide is an attractive oxidant that might be used in such cycles to install C-NO_2 groups. We therefore explored the reactivity of $Pd(\kappa^2\text{-}2\text{-}C_6H_4py)_2$, itself formed by C-H activation of 2-phenylpyridine, as a prototypical substrate for such reactions. Oxidation does take place, but the product is the nitro-nitr*ato* palladium(IV) complex $(\kappa^2\text{-}2\text{-}C_6H_4py)_2Pd(NO_2)(NO_3)$. The facile disproportionation of NO_2 in this case illustrates a complication of using nitrogen dioxide that is absent in the reactions of more traditional oxidants. The isolated product does contain both Pd-aryl and Pd-NO_2 bonds, but no reductive elimination is seen even under forcing conditions.



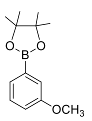
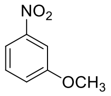
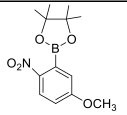
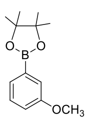
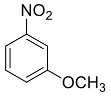
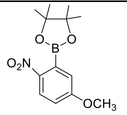
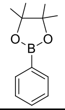
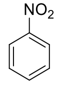
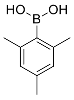
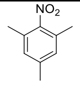
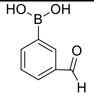
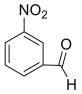
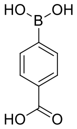
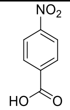
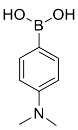
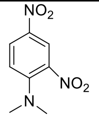
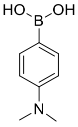
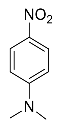


Development of Bismuth-Based Catalysts for C-H Activation. While transition-metal catalysts for C-H activation have become well-established, there is considerable interest in better developing main group compounds to achieve this goal as well. Heavy *p*-block elements such as mercury, thallium, and lead have shown promising reactivity but have obvious drawbacks (high toxicity). In contrast, bismuth has remarkably low toxicity (Pepto-Bismol® is a bismuth salt). The problem is that Bi(V) is relatively difficult to stabilize. We have developed several bismuth(III) compounds, with both high coordination numbers (seven-coordinate $N[CH_2CH_2N{=}CHC_6H_2{}^{t}Bu_2O]_3Bi$) and low coordination numbers (four-coordinate $PhBi[OC_6H_2{}^{t}Bu_2N{=}CHC_6H_2{}^{t}Bu_2O]$) as potential precatalysts for Bi(V)-mediated substrate activation (ideally with NO_2 as oxidant). The former can be oxidized to Bi(V), but the products of oxidation do not react with C-H bonds. The latter undergoes oxidative cyclization of the ligand on attempted oxidation, forming a benzoxazole and deactivating the putative catalyst.





Nitrative *ipso*-Deboronation of Arylboronic Acids and their Pinacol Esters. Carbon-boron bonds, particularly arylboronic acids and their derivatives, have become powerful and versatile synthons thanks to a wide variety of metal-catalyzed methods. They can be installed (generally as their pinacol esters) by efficient iridium-catalyzed undirected aryl C-H activation. They can then be used to make a wide variety of new bonds to carbon. The most well-known such transformation is the Suzuki coupling, used to make C–C bonds, but other methods have been developed to form aryl ethers or anilines from arylboronates. The transformation to the nitro group is less well-studied, and methods of doing so using N_2O_4 had not been published. This would be particularly interesting as a route to nitroaromatics since the sterically determined selectivity exhibited in borylation of arenes would complement the electronic selectivity (for electron-rich positions) shown by traditional electrophilic nitration.

Substrate	Catalyst, conditions	Product, yield
	none, 90 ºC, 19 h	  6% 31%
	$IrCl_3(py)_3$, 90 ºC, 3 d	  65% 9%
	none, 90 ºC, 3d	 93%
	none, 90 ºC, 2 h	 73%
	none, RT, 3 h	 99%
	90 ºC, 3d	 no cat, 7% cat, 88%
	none, RT, 1 h, 5 equiv NO_2	 93 %
	none, RT, 1 h, 1 equiv NO_2	 81 %

We started out by examining 3-methoxyphenylboronic acid pinacol ester, as it promised to be a particularly challenging substrate, with the methoxy group directing aromatic nitration *ortho* and *para*, and the Bpin group generally less reactive than the $B(OH)_2$ group.

Indeed, uncatalyzed reaction with N_2O_4 results principally in electrophilic nitration. However, a number of transition metal catalysts result in suppression of the electrophilic pathway and give 3-nitroanisole, the product of *ipso* nitro-deboronation, in reasonable yields. Trichlorotris(pyridine)iridium(III) is the most selective catalyst for this reaction. The reaction also works well for a number of other boronic acids and boronate esters, with good tolerance of ancillary functional groups. In some arylboronic acids, nitrative deboronation is facile without a catalyst, but where the uncatalyzed reaction fails, $IrCl_3(py)_3$ is generally an effective catalyst. Highly electron-rich substrates such as 4-dimethylaminophenylboronic acid are susceptible to over-nitration, but this can be controlled by use of limited amounts of nitrogen dioxide. This reaction thus constitutes a synthetically useful method for installing nitro groups on arylboronates, and by extension, arenes.

Publications. Three publications are anticipated from this work:

Roche, Tierney K.; Kidd, Arnold B.; Forrest, Ryan P.; Brown, Seth N. "Mechanism and Selectivity of Reductive Elimination from Trimethyl(nitro)platinum(IV) Complexes." In preparation.

Cui, Jinlan; Brown, Seth N. "Preparation, Characterization, and Reactivity of Arylpalladium(II) Nitrite Complexes." In preparation.

Cui, Jinlan; Kidd, Arnold B.; Zheng, Qinheng; Brown, Seth N. "Catalyzed and Uncatalyzed Nitrative Deboronation of Arylboronic Acids and Their Pinacol Esters Using Nitrogen Dioxide." In preparation.