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Practical Olefin Aziridination with a Broad Substrate Scope

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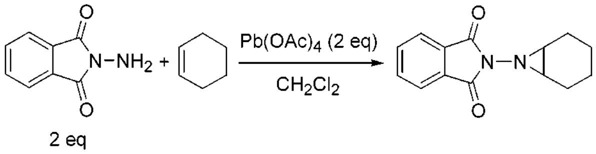
Received October 3, 2001; Revised Manuscript Received November 27, 2001

Organic compounds participate in two main kinds of transformations: carbon−carbon bond forming processes and reactions accompanied with changes in the oxidation states at carbon atoms.[1] The oxidation reactions are carried out using appropriate electron or atom transfer reagents such as metal derivatives (e.g., OsO_4, CrO_3, $KMnO_4$, MnO_2, $K_3Fe(CN)_4$, $Pb(OAc)_4$) or other oxidants (e.g., Cl_2, NaOCl, H_2O_2, O_2, $KHSO_5$). Despite the high levels of selectivity these reagents can offer, the majority produce toxic waste. The development of waste-free technologies is one of the daunting challenges that faces chemists,[2] and new approaches that eliminate the toxic byproducts of oxidation reactions are needed.

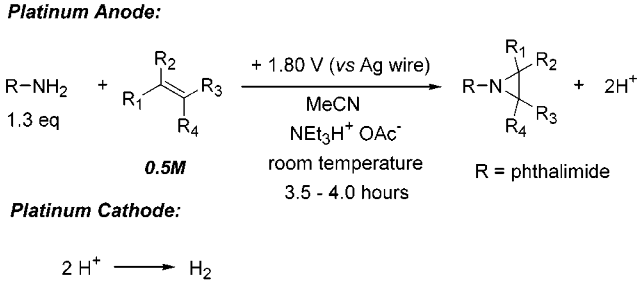
Electrochemistry, a branch of science that studies direct electron transfer at electrode surfaces, is frequently referred to as one of the prototypical green technologies of the future.[2d] Selectivity in the electrosynthesis of organic compounds can be obtained by subjecting reactants to oxidizing or reducing environments of specific and invariant electrochemical potential.[3] Our goal is to find general and practical electrochemical solutions to the selective functionalization of hydrocarbons.[4] Aziridination of olefins is of particular interest due to the enormous synthetic potential of aziridines.[5] These nitrogen-containing heterocycles have 28 kcal/mol of strain[6] and are amenable to ring-opening reactions with a wide range of nucleophiles. Such transformations lead to molecules with valuable 1,2 heteroatom relationships, commonly found in natural products and in pharmaceuticals.[7] Olefin aziridination reactions are usually accomplished via metal-mediated transfer of a nitrene fragment to the olefin.[8] The corresponding processes produce a variety of byproducts that stem from metal additives and from oxidants.

To date, there are no examples of catalytic oxidation systems based on readily available oxidants that (1) convert simple amines or amides into active nitrogen transfer species in the presence of olefins and (2) leave no byproducts. Here we show that these important challenges can be met electrochemically without metal-based reagents, catalysts, and stoichiometric oxidants. We describe an aziridination process that delivers a nitrogen-containing functionality to a broad range of olefins from a readily available amine. The continuum of applied potentials and the heterogeneous nature of reactions at electrode surfaces allow for the electrochemical discrimination of substrates which have similar redox potentials and therefore cannot be selectively reduced or oxidized using soluble reagents. This selectivity is due to the phenomenon of *overpotential*,[9] the kinetic inhibition of electron transfer on a particular electrode surface.



(1)

Scheme 1



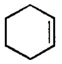
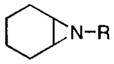
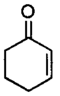
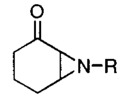
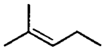
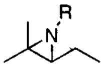
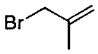
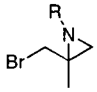
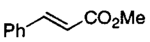
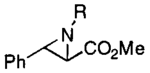
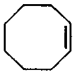
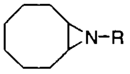
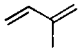
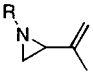
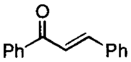
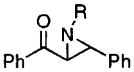
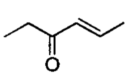
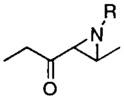
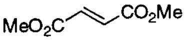
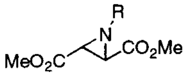
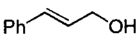
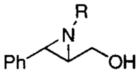
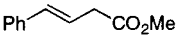
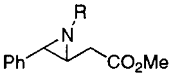
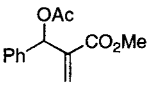
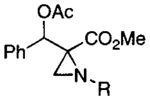
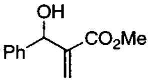
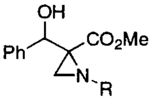
We focused our attention on finding alternative routes for reactions that typically involve stoichiometric amounts of highly toxic lead(IV) oxidants.[10] Lead tetraacetate-promoted aziridination of olefins with *N*-amino derivatives (eq 1) is a valuable synthetic transformation,[11] but its widespread application is hampered by the use of large amounts of $Pb(OAc)_4$. We started by investigating the feasibility of reducing the amount of $Pb(OAc)_4$ to catalytic quantities. The cyclic voltammetry (CV) of $Pb(OAc)_2$ in acetonitrile gives the value of +1.60 V (vs Ag/AgCl) for the oxidation potential of Pb^{2+} to Pb^{4+},[12] whereas the CV of *N*-aminophthalimide (0.01 M in acetonitrile) shows two irreversible one-electron oxidation processes with anodic peak potentials at +1.35 V and at +1.68 V (vs Ag/AgCl).[13] It was therefore possible to perform the aziridination of cyclohexene with only 10 mol % $Pb(OAc)_4$ by reoxidizing Pb^{2+} to Pb^{4+} electrochemically at +1.60 V.

Furthermore, we discovered that the CV of cyclohexene (0.01 M in acetonitrile) produces an anodic current of $-1.0\ \mu$A at +1.68 V (vs Ag/AgCl), which is only a small fraction of the current recorded for *N*-aminphthalimide ($-152\ \mu$A). This indicates that the background oxidation of olefins on a platinum electrode is kinetically disfavored due to olefin overpotential. We reasoned that a direct electrochemical nitrogen transfer process should take place at around +1.60 V *in the absence of even catalytic amounts of* $Pb(OAc)_4$. Indeed, we have observed that a simple combination of platinum electrodes, triethylamine, and acetic acid leads to a highly efficient formal nitrene transfer[14] from *N*-aminophthalimide to cyclohexene (Scheme 1). The reaction utilizes only a small excess of *N*-aminophthalimide relative to the olefin and can be performed in a divided cell using a silver wire as a pseudo-reference electrode.

Optimization of the working potential revealed that +1.80 V versus Ag wire[15] produced the highest isolated yield of the aziridine from cyclohexene (Table 1, entry 1). Additional increases in the working potential were detrimental to the yield due to the background oxidation of cyclohexene. Temperature changes had negligible effect on the efficiency of nitrene transfer. No special precautions to exclude moisture or air were taken. The reaction was stopped when the cell current dropped to less than 5% of its original value. Table 1 illustrates the wide substrate scope of this process. Remarkably, both electron-rich and electron-poor olefins are converted to aziridines with high efficiency. The aziridination

10.1021/ja0172215 CCC: $22.00

Table 1. Electrochemical Aziridination of Olefins

Entry	Substrate	Product	Isolated Yield, %
1			85
2			78
3			91
4			42
5			86
6			85
7			51[a]
8			83
9			93
10			92
11			81
12			55
13			79[b]
14			73[c]

[a] Reaction was conducted at 0 °C. [b] 2:1 ratio of diastereomers. [c] 4.4:1 ratio of diastereomers.

can be performed on a multigram scale, and even larger scales should be accessible using readily available flow cells.[3a] A wide variety of substrates other than olefins can also be considered as suitable nitrene acceptors.[16] Other amines or hydrazines may also be used as precursors to nitrene transfer agents and are within the scope of our future studies.

In summary, our study illustrates the possibility of a rational approach that bypasses the requirement for stoichiometric amounts of toxic oxidants and metal additives in organic redox reactions.[17] The continuum of redox potentials provided by electrochemistry and the possibility of differentiating substrates on the basis of their overpotentials should be a guide to other examples of highly selective and practical organic reactions. It is now possible to develop a set of guidelines for emulating a variety of metal-based redox processes via optimization of reaction conditions (such as nature of electrode, applied potential, additives, etc.) with the goal of maximizing the difference in overpotentials between the reacting molecules.[18]

Acknowledgment. We thank the National Science and Engineering Research Council (NSERC), Canada Foundation for Innovation, ORDCF, and the University of Toronto for financial support. Andrei Yudin is a Cottrell Scholar of Research Corporation. We are grateful to Professors M. G. Finn, Robert H. Grubbs, and K. Barry Sharpless for reading the manuscript, helpful discussions, and encouragement. Ms. Shahla Yekta and Mr. Yu Chen are acknowledged for preparing some of the olefins (entries 12−14).

Supporting Information Available: Experimental procedures and characterization data for the aziridines (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Preliminary mechanistic investigation indicates that this electrochemical aziridination is stereospecific. For instance, aziridination of the benzyl ether of *cis*-2-hexen-1-ol resulted in exclusive formation of the *cis*-aziridine. In addition, phthalimide has been identified as the only byproduct of this reaction (for a study of nitrene decompositionn pathways that lead to phthalimide, see: Hoesch, L.; Koppel, B. *Helv. Chim. Acta* **1981**, *84*, 864). Although other mechanistic possibilities cannot be ruled out at this point, these observations support a nitrene intermediate.

(15) Silver wire pseudo-reference electrode was calibrated against the ferrocene/ferricinium couple in the electrolysis medium ($E_{pa} = 0.47$ V, $E_{pc} = 0.30$ V).

(16) Our preliminary results indicate that under similar conditions a variety of sulfoxides participate in a highly efficient sulfoximination reaction.

(17) Ironically, the industrial origin of all readily available inorganic oxidants is electrochemistry. For instance, approximately 3% of electricity in the United States is spent annually on the production of chlorine.

(18) The aziridination reaction did not take place when the platinum anode was replaced by graphite. In a marked contrast to the platinum case, our CV study on carbon revealed that anodic current corresponding to the background oxidation of cyclohexene (-5.3 μA) was comparable to the current corresponding to the oxidation of *N*-aminophthalimide (-15.6 μA). Such a small difference in the rate of electrochemical oxidation apparently does not secure high selectivity in olefin aziridination.

JA0172215