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New methods for the synthesis of heterocyclic compounds

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Abstract: Due to frequent occurrence of nitrogen-containing groups among the biologically active compounds, chemos elective functionalization of organic molecules with nitrogen-con- taining functional groups is an important area of organic synthesis. We have proposed and implemented a new strategy toward design of nitrogen-transfer reactions on inert electrode surfaces with a particular focus on the generation and trapping of highly reactive nitrogen- transfer agents. A wide range of structurally dissimilar olefins can be readily transformed into the corresponding aziridines. The resulting aziridines are precursors to a range of cata- lysts via nucleophilic ring-opening with diaryl- and dialkyl phosphines. Another strategy ex- plored in the context of oxidative nitrogen transfer is cycloamination of olefins using NH aziridines.

INTRODUCTION

The transformations of organic compounds belong to one of the following two broad categories: car- bon–carbon bond-forming reactions and redox processes. Over the years, remarkable progress has been achieved in design and applications of novel metal-based complexes in oxidation chemistry. The metal center of such a catalyst is surrounded by a ligand, which resembles and emulates the function of the enzyme active site. This strategy is known to adequately address the issues of regio-, chemo-, and stereoselectivity in a number of synthetic transformations. The use of nitrogen-based oxidants allows for oxidation-driven nitrogen transfer, which is unprecedented in Nature. Because of the fundamental role of electron transfer in redox processes, we recently became interested in developing an *electro- chemical* understanding of oxidative atom-transfer reactions. The ultimate goal is to find general and practical electrochemical solutions to the selective functionalization of hydrocarbons. Development of such understanding may lead to optimal processes with regard to the nature of stoichiometric oxidants. Understanding ways of electrochemical generation of highly reactive atom-transfer species would be of particular interest.

ELECTROCHEMICAL AZIRIDINATION OF OLEFINS

The aziridination of olefins is of particular interest due to the synthetic value of aziridines [1]. These nitrogen-containing heterocycles have 28 kcal/mol of strain [2] and are amenable to ring-opening reac- tions with a wide range of nucleophiles. Such transformations lead to the molecules with valuable 1,2-heteroatom relationships [3]. Synthetic methodologies for the preparation of aziridines include: (1) nitrene addition to olefins [4]; (2) carbene [5] and ylid [6] addition to imines; and (3) cyclization of 1,2-aminoalcohols, 1,2-aminohalides, and 1,2-azidoalcohols [7]. Olefin aziridination reactions are typ- ically accomplished via metal-mediated transfer of a nitrene fragment to the olefin [8]. These metal-cat- alyzed reactions originate from Mansuy's study on the Fe-porphyrin and Mn-porphyrin complexes [9]. Since the mid-1990s, many research groups have utilized metal-stabilized nitrenes in olefin aziridina- tion. The right choice of the stoichiometric oxidant, which acts as nitrogen source, is required in order to efficiently drive a given catalytic reaction. Evans and Jacobsen utilized TsN=IPh as the nitrogen source and Cu(I) or Cu(II) salts such as $Cu(MeCN)_4ClO_4$, CuOTf, or $Cu(acac)_2$ as catalysts [10]. Both Evans [11] and Jacobsen [8b] groups later developed Cu-based chiral catalysts to achieve enantio- selective aziridination. Katsuki [8d] investigated the use of optically active Mn(III)-salen complexes in olefin aziridination. Other metal-based catalysts include Rh(II), developed by Müller [8e], and methyl- trioxorhenium (MTO), studied by Nguyen [8f]. Until recently, there have been no examples of catalytic oxidation systems based on readily available oxidants that convert amines or amides into active nitro- gen-transfer species in the presence of olefins and leave no by-products. On the other hand, a stoichio- metric oxidation system that generates nitrene precursor from the amine species, does exist. Valuable aziridines equipped with an N–N bond can be obtained from olefins using lead tetraacetate as oxidant [12]. Unfortunately, widespread application of this method is hampered by the use of excess $Pb(OAc)_4$, known for its high toxicity [13]. We first used cyclic voltammetry (CV) to study the

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$Pb(OAc)_4$-medi- ated nitrene-transfer system. The CV of $Pb(OAc)_2$ in acetonitrile gives a value of +1.60 V (vs. Ag/AgCl) for the oxidation potential of Pb(II) to Pb(IV), whereas the CV of *N*-aminophthalimide (0.01 M in acetonitrile) shows two irreversible one-electron oxidation processes with anodic peak po- tentials at +1.35 and +1.68 V (vs. Ag/AgCl). The readiness of oxidizing $Pb(OAc)_2$ encouraged us to run the electrochemical aziridination with a catalytic amount of $Pb(OAc)_2$. Using 10 mol % $Pb(OAc)_2$ with respect to *N*-aminophthalimide, cyclohexene (1.5 equiv) was transformed into the aziridine at a constant potential of +1.80 V (Ag wire pseudo-reference electrode), and gave a 75 % isolated yield of **1**. The rel- ative facility with which olefins undergo anodic oxidation prompted us to record the CV of cyclohexene [14] under the conditions used in *N*-aminophthalimide oxidation (0.01 M in acetonitrile). We observed an anodic current of –1.3 □A at +1.68 V (vs. Ag/AgCl), which is only a small fraction of the current recorded for *N*-aminophthalimide (–152 □A, Fig. 1). This suggests that the background oxidation of olefins on a platinum electrode is disfavored under the reaction conditions due to olefin overpotential. By definition, overpotential is the "additional potential (beyond the thermodynamic requirement) needed to drive a reaction at a certain rate" [15]. Under certain conditions (i.e., electrode material and

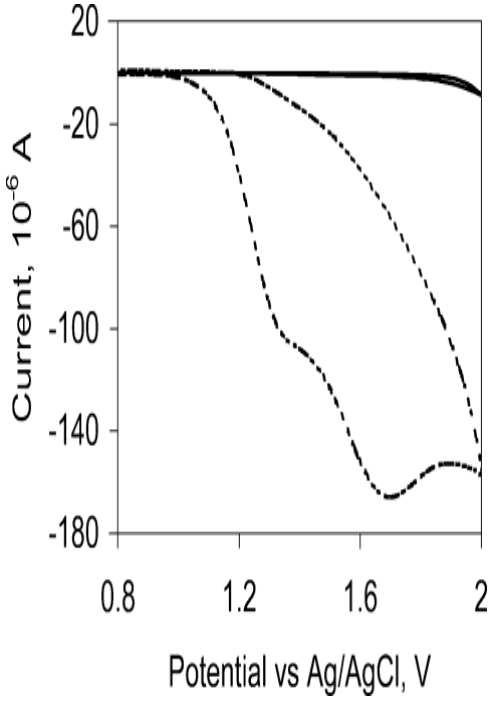

Fig. 1 Cyclic voltammetry of *N*-aminophthalimide (dashed line) and cyclohexene (solid line) in acetonitrile with M HEt_3NOAc on platinum electrode.

medium), various substrates possess different overpotentials. Based on our study, we propose that this phenomenon can be used as a guiding principle to selectively oxidize a given species in the presence of a thermodynamically similar acceptor molecule without detrimental background reactions. Therefore, selective oxidation of *N*-aminophthalimide directly at the anode at around +1.60 V, should be possible *in the absence of even catalytic amounts of* $Pb(OAc)_4$. Indeed, we have found that a simple combina- tion of platinum electrodes, triethylamine, and acetic acid leads to a highly efficient, room-temperature nitrene transfer from *N*-aminophthalimide to cyclohexene (Scheme 1).

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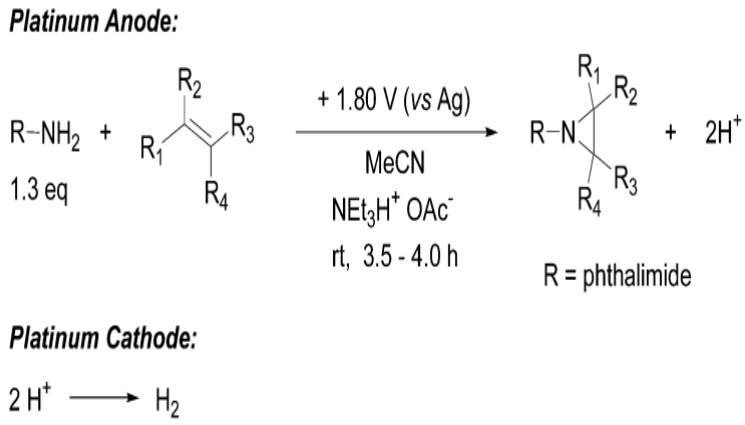

Scheme 1 Electrochemical aziridination of olefins.

The reaction utilizes only a small excess of *N*-aminophthalimide relative to the olefin and can be performed in a divided cell using silver wire as a pseudo-reference electrode. The scope of this electrochemical aziridination process is outlined in Table 1. In a sharp contrast to the metal-based nitrogen transfer, both electron-rich and -poor olefins are converted to aziridines with high efficiency under our conditions. For certain monosubstituted terminal olefins, the electrochemical aziridination was not suc- cessful although the redox behavior of these olefins is not significantly different from others. Surprisingly, the *cis*-olefin dimethyl maleate was found to be inert toward electrochemical aziridination, while the *trans*-isomer, dimethyl fumarate, gave excellent yield of the aziridine (Table 1, entry 10). In all cases with inert olefins, *N*-aminophthalimide was completely converted to phthalimide (precipitated from the reaction mixture) and the olefins were recovered quantitatively. This indicates that the elec- trochemical oxidation process does take place, but the active nitrogen-transfer species does not react with the olefin.

We also investigated the role of electrode material, which is well known to be critical in electrosynthesis. For instance, the Kolbe reaction requires smooth platinum or iridium electrode to give the coupling product, whereas graphite and porous carbon anode lead to the products that are exclusively derived from carbenium ions [16]. In our case, the aziridination reaction did not take place when the platinum anode was replaced by graphite. The CV study on carbon electrode revealed that anodic current corresponding to the oxidation of cyclohexene (–5.3 □A at +1.68 V) was comparable to that of *N*aminophthalimide (–15.6 □A at +1.68 V). Such a small difference in electroactivity apparently does not secure high selectivity in olefin aziridination.

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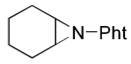
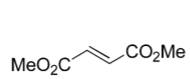
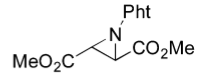
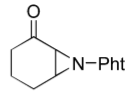
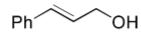
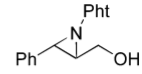
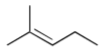
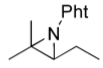
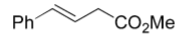
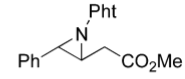
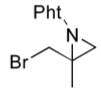
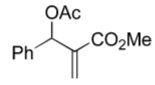
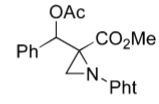
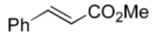
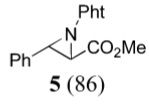
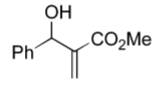
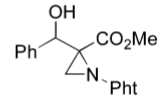
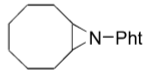
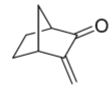
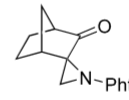
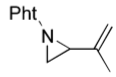
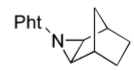
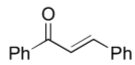
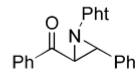
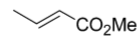
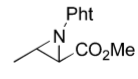
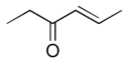
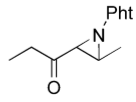
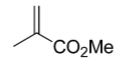
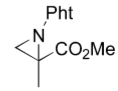
Table 1 Electrochemical aziridination of olefins.

Entry	Substrate	Product (yield, %)	Entry	Substrate	Product (yield, %)
1		 **1** (85)	10		 **10** (92)
2		 **2** (78)	11		 **11** (81)
3		 **3** (91)	12		 **12** (55)
4		 **4** (42)	13		 **13** (79^b)
5		 **5** (86)	14		 **14** (73^c)
6		 **6** (85)	15		 **15** (82^d)
7		 **7** (51^a)	16		 **16** (80^e)
8		 **8** (83)	17		 **17** (88)
9		 **9** (93)	18		 **18** (90)

[a]Reaction at 0 □C. [b]2:1 ratio of diastereomers, determined from ^{1}H NMR integration of the acetyl protons at 2.15 and 2.10 ppm. [c]4.4:1 ratio of diastereomers, determined from ^{1}H NMR integration of the benzyl proton at 5.16 and 5.70 ppm. [d]Ca. 1.5:1 ratio of diastereomers, determined from ^{1}H NMR integration of the phthalimido-protons at 7.65 and 7.73 ppm.

[e]Single diastereomer, as determined by ^{1}H NMR.

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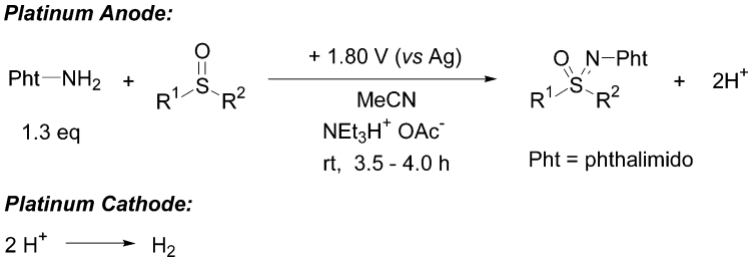
Electrochemical imination of sulfoxides

The nitrene transfer to sulfur was investigated in a similar way to aziridination [17]. At +1.68 V, tetramethylene sulfoxide (0.01 M in acetonitrile) produces a considerably smaller anodic current of –7.52 □A than the current recorded for *N*-aminophthalimide (–152 □A). This is a sign of a kinetically sluggish background oxidation of sulfoxides to sulfones on a platinum electrode [1].

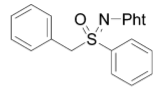
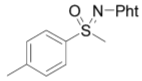
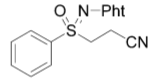
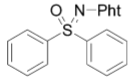
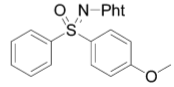
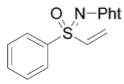
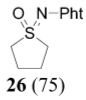
The nature of electrode material is crucial to the success of this process as well. The CV of tetramethylene sulfoxide (0.01 M in acetonitrile) on a glassy carbon electrode shows two irreversible oxidation processes with peak potentials at +1.64 and +1.82 V and a much higher anodic current (–272 □A) than that of *N*-aminophthalimide at +1.68 V (–15.6 □A). Therefore, the bulk electrolysis of tetramethylene sulfoxide in the presence of *N*-aminophthalimide on a graphite anode gave tetramethylene sulfone as the major product with no evidence of sulfoximine formation. On the platinum anode, the electrolysis conditions were similar to those of aziridination (Scheme 2).



Scheme 2 Electrochemical sulfoximination.

A small excess of *N*-aminophthalimide relative to the sulfoxide was used. The electrolysis was performed in a divided cell using a silver wire as a pseudo-reference electrode, which was calibrated against the ferrocene/ferricinium couple in the electrolysis medium (E_{pa} = 0.47 V, E_{pc} = 0.30 V). Table 2 illustrates the substrate scope of this process.

Table 2 Electrochemical synthesis of *N*-phthalimido sulfoximines.

Entry	*N*-phthalimido sulfoximine (yield, %)	Entry	*N*-phthalimido sulfoximine (yield, %)
1	 **19** (76)	5	 **23** (86)
2	 **20** (62)	6	 **24** (81)
3	 **21** (83)	7	 **25** (88)
4	 **22** (70)	8	 **26** (75)

For sulfoxide **22** (Table 2, entry 4), no aziridination product was observed, indicating the possibility to achieve chemoselective nitrene transfer to the sulfoxide moiety. There was no evidence for the background formation of the sulfone by-product. The electrochemical nitrene-transfer process was found to be stereospecific. An enantiomerically enriched (93 % ee of the *R*-enantiomer) sample of methyl *p*-tolyl sulfoxide was electrolyzed under the same conditions as above. The ee value measured for the product

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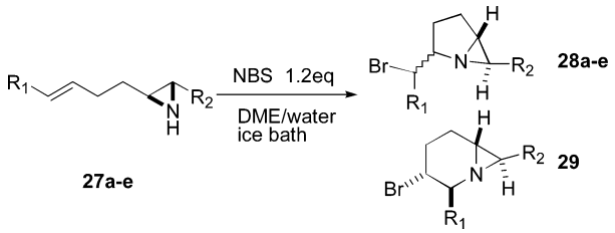
sulfoximine **20** was the same (97 %) within the error of HPLC analysis and the X-ray structure of the product showed retention of configuration, indicating that no racemization occurred during nitrene transfer process.

APPLICATIONS OF AZIRIDINES IN OXIDATIVE NITROGEN TRANSFER TO OLEFINS

Our interest in synthetic applications of functionalized aziridines [18] has led to the investigation of their utility in the synthesis of larger nitrogen-containing heterocycles. Known for the difficulties in controlling their reactivity, aziridines are rarely used in complex molecule synthesis [19]. If functional- ization of an aziridine-containing building block is required during synthesis, nitrogen protection/de- protection sequences are unlikely to be successful due to aziridines' susceptibility to acidic reagents and harsh reaction conditions. We reasoned that despite its basic character, aziridine nitrogen should be quite resistant to oxidative degradation so that transformations of aziridine-containing building blocks can be realized. At the outset of our investigations, we had observed a significant (0.8 V) difference in the oxidation potential of cyclohexene imine compared to the value recorded for a typical secondary amine such as piperidine, known for its low stability toward oxidation [20].

The aziridine-containing building blocks were synthesized from commercially available starting materials. The NH portion of **27a** is separated from the olefin by the $(CH_2)_2$ linker, positioned toward cyclization to give pyrrolidine- and piperidine-containing heterocycles. The pyrrolidine and piperidine rings are incorporated into the structures of a wide range of natural products and pharmaceuticals, which makes them an important class of targets for stereoselective synthesis [21]. If relative stereo-chemistry of the products can be controlled during cyclization and subsequent ring-opening steps, the oxidative aziridine cycloamination methodology should be a valuable addition to the established meth-ods [22].

Our studies revealed that aziridines **27** are converted into 1-azabicyclo[3.1.0]hexane derivatives **28** in good yields upon treatment with *N*-bromosuccinimide (NBS) in DME/water [23]. The thin-layer chromatography (TLC) analysis indicated complete conversion of the NH aziridine to the correspon-ding N-Br species within the first 2 min of the reaction [24]. The bromamine **27f** thus formed attacked the double bond of the molecule to give the cycloamination product (Scheme 3). Table 3 shows the scope of the reaction. The products are [5,3] bicyclic rings in the case of the terminal double bond-con- taining substrates, whereas aryl-substituted double bonds preferentially give six-membered ring prod- ucts.



Scheme 3 Reactivity of aziridines **27** in the presence of NBS.

Table 3 Intramolecular cycloamination of olefins.

Entry	R_1	R_2	Product[b]	Yield[a]
1	H	PhCO	**28a**	76
2	Me	PhCO	**28b**	51
3	CH_2OH	PhCO	**28c**	54
4	Ph	PhCO	**29d**c	67
5	H	PhCH(OH)	**28e**	55

[a]The diastereomeric ratios were as follows: for **28a**, 41:59; for **28b**, 33:67; for **28c**, 33:67; for **29d**, 19:81.

[b]Structures were determined by NMR analysis (NOE, HMBC, and COSY). [c]23 % of **28d** was also isolated.

The resulting bicycles **28** were converted into *exo*-methylene bicyclic aziridines **30** in quantitative yields by dehydrobromination (Scheme 4). We attribute surprisingly high stability of the

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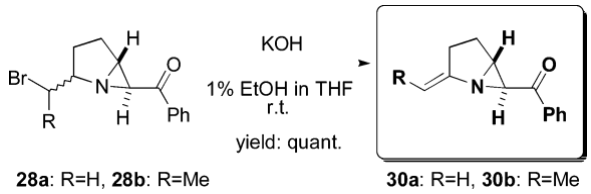
resulting enamines to the orthogonal orientation of the nitrogen electron pair in relation to the double bond, evi- dent from the single-crystal X-ray analysis. The X-ray data shows that the bond length between C(6A) and C(7A) is 1.32 Å, which is typical of an olefin system. Worthy of note, this interesting and uncom- mon structural motif is present in the azinomycin family of antibiotics [25]. The bicyclic aziridine **30**possesses considerable synthetic potential because of the enamine-like aziridine ring that can be trans- formed into an imine/enamine upon ring-opening. The ring-opening reactions proceed with high yields and excellent diastereoselectivities. The reactions are regioselective and afford the corresponding pyrro- lidine derivatives.



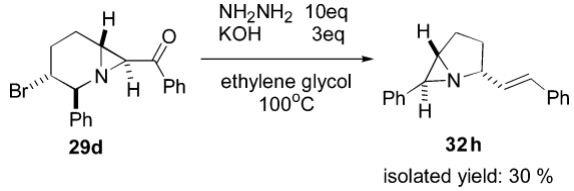
Scheme 4 Formation of *exo*-methylene bicyclic aziridines.

The resulting enamines are in situ tautomerized into cyclic imines. The reductive ring-opening of aziridine **30a** by hydrogen on Pd/C gives five-membered cyclic imine in excellent yield (Table 4, entry 5).

Table 4 Ring-opening reactions of bicyclic aziridines **30**.

Entry	R_1	Condition	R_2	Yield
1	H	$TMSN_3$ 2 eq, H_2O 10 eq, in DCM, r.t.	N_3	99
2	Me	$TMSN_3$ 2 eq, H_2O 10 eq, in DCM, r.t.	N_3	95
3	H	HBF_4 1.5 eq, in MeOH, r.t.	OMe	65
4	H	AcOH 5 eq, in DCM, r.t.	OAc	73
5	H	10 % Pd/C 0.1 wt, H_2, in MeOH, r.t.	H	99

Aziridine ring-opening was also triggered under the reductive conditions. Upon treatment with hydrazine, valuable 2-allylamine derivatives were obtained in good yields (Scheme 5). The resulting cyclic imines can be readily reduced to pyrrolidines using DIBAL.



Scheme 5 Synthesis of allylamines **31**.

DESIGN AND DEVELOPMENT OF CYCLOHEXANE-BASED *P,N*-LIGANDS FOR TRANSITION-METAL CATALYSIS

Bidentate ligands are ubiquitous components of many transition metal-based catalysts [26]. Among them, chiral *P,N*-ligands have found applications in a variety of asymmetric processes ranging from

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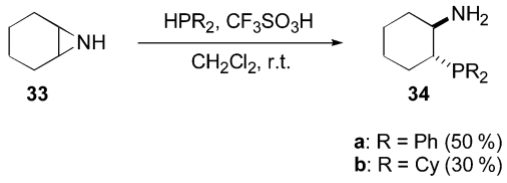
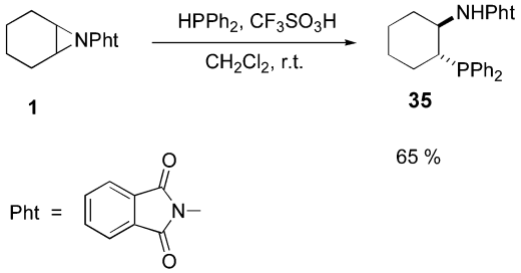
al- lylic substitution to hydrogenation of ketones [27,28]. From the reactivity standpoint, a *P,N*-ligand con- tains a combination of hard (nitrogen) and soft (phosphorus) centers [27c]. Within this environment, metal ions can be stabilized in their low-oxidation states by the □-accepting character of the softer phos- phorous site. On the other hand, high-oxidation states are better stabilized by the harder nitrogen site [27d,29]. This combination of complementary properties of nitrogen and phosphorous has been ex- plored in a number of carbocyclic environments. For instance, in a recent example reported by Jones [30], the hemilabile character of (dialkylphosphino)dialkylaminoethane was found to be crucial for the catalytic activity of the derived platinum complexes. The formation of putative five-membered metal- lacycles in this system was not observed in the presence of chelating diphosphine ligands. We were puz- zled by the absence of examples of *P,N*-ligands based on the *trans*-1,2-cyclohexane fragment. The cyclohexane template is present in a number of useful chiral ligands for asymmetric catalysis [31] due to its ability to rigidify the trans configuration of substituents. We therefore viewed this as an opportu- nity to explore new catalytic activity. Our interest in the synthesis and applications of functionalized aziridines [18a] prompted us to investigate their ring-opening with phosphine nucleophiles. Readily available 7-azabicyclo[4.1.0]heptane (**32**) [32] was subjected to nucleophilic ring-opening with diphenylphosphine according to Scheme 6, yielding *trans*-1-amino-2-diphenylphosphino cyclohexane (**34a**) in 50 % yield.



Scheme 6 Ring-opening of aziridine **32** with diphenylphosphine.

The use of trifluoromethanesulfonic (triflic) acid was crucial in order to activate the aziridine ring toward opening. When trifluoroacetic acid was utilized in place of triflic acid, rapid oxidation of the phosphorous center was observed [33]. Analogously, the opening of aziridine **33** by using dicyclo- hexylphosphine as a nucleophile led to the formation of *trans*-1-amino-2-dicyclohexylphosphino- cyclohexane (**34b**) as a white solid in 30 % yield (Scheme 6). This opens up to the possibility of syn- thesizing a wide variety of *P,N*-ligands with different kinds of disubstituted phosphines. The results ob- tained in parent aziridine ring-opening led us to investigate other derivatives of cyclohexene aziridine, such as 2-(7-azabicyclo[4.1.0]hept-7-yl)-1*H*-isoindole-1,3(2*H*)-dione (**1**), readily available through electrosynthesis (Table 1) [18a]. We subjected aziridine **1** to ring opening with diphenylphosphine under the same conditions as for **33**. Accordingly, 2-{[2- (diphenylphosphino)cyclohexyl]amino}-1*H*- isoindole-1,3(2*H*)-dione (**35**) was obtained in 65 % yield (Scheme 7).



Scheme 7 Ring-opening of aziridine **1** with diphenylphospine.

The ligand **34a** was successfully resolved using (*D*)-tartaric acid via the formation of the tartrate salt, which was filtered and recrystallized from water. X-ray analysis carried out on crystals grown in 95 % aqueous ethanol showed that the enantiomer separated from the racemic mixture had (*R,R*) ab-

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solute configuration. The enantiomerically pure *P,N*-ligand was then recovered by dissolving the tartrate salt in 10 % sodium hydroxide solution and extracting the mixture with dichloromethane.

The enantiomeric excess of the recovered ligand (>99 %, 65 % yield) was analyzed by converting it into Mosher acid amide [34]. Throughout these manipulations, the *P,N* derivatives showed considerable stability toward air oxidation. When a solution of **34a** in $CDCl_3$ was stirred under air for 16 h, less than 4 % oxidation was observed. In summary, the cyclohexane-based *P,N*-ligands can be prepared in enantiomerically pure form from readily available aziridines and are precursors to active catalysts. Straightforward manipulation of substituents on nitrogen renders these ligands applicable in asymmet- ric catalysis. A particularly useful property of these ligands is significant oxidative stability of the phos- phorus center. The choice of phosphine during the ring-opening step allows one to manipulate elec- tronic properties of the system.

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