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Aziridination of alkenes with N-substituted hydrazines mediated by iodobenzene diacetate

Jiayin Li,[a] Jiang-Lin Liang,[b] Philip Wai Hong Chan[b] and Chi-Ming Che[a,b,*]

[a]*Shanghai-Hong Kong Joint Laboratory on Chemical Synthesis, Shanghai Institute of Organic Synthesis, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China*

[b]*Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis, The University of Hong Kong, Pokfulam Road, Hong Kong, PR China*

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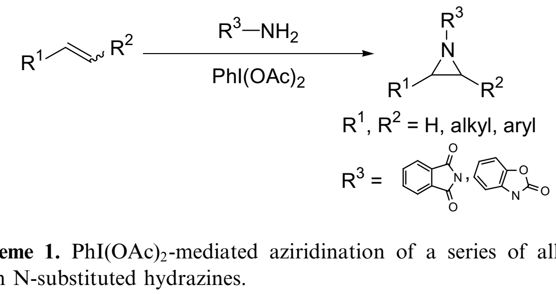
Abstract—Aziridination of a variety of alkenes with N-substituted hydrazines mediated by iodobenzene diacetate under mild conditions (K_2CO_3, CH_2Cl_2) and ambient temperature were achieved in good to excellent yields (up to 99%), and conversions. The practicality and simplicity of this C–N bond formation protocol was exemplified by its application to the aziridination of cholesteryl acetate in a stereoselective manner.

The ability of aziridines to undergo regio- and stereoselective ring opening reactions renders them invaluable building blocks in organic synthesis.[1] The aziridine structural unit itself is found in a number of bioactive products such as mitomycins and azinomycins.[1,2] Despite this, studies on C–N bond formations, particularly those involving amidation of saturated C–H bonds and aziridination of C=C bonds remain sparse. Recent studies by us[3] and others[4] demonstrated the simplicity and versatility of transition-metal catalysts for nitrene transfer reactions. Work in our laboratory found that iodobenzene diacetate {$PhI(OAc)_2$} and RNH_2 (R = *p*-$MeC_6H_6SO_2$, *p*-$NO_2C_6H_6SO_2$) could be used directly as a nitrogen source in ruthenium(II) porphyrin-catalyzed inter- and intramolecular amidation processes.[3a,e] More recently, we reported extension of the '$PhI(OAc)_2$ + RNH_2' amidation protocol to the intramolecular aziridination of acyclic sulfonamides catalyzed by rhodium(II,II) dimers.[5]

Atkinson et al. showed that reactions of alkenes in the presence of lead(IV) acetate (LTA) and chiral *N*-aminoquinazolinones gave the desired aziridines with high diastereoselectivity.[1d,6] More recent works by Vederas[7] and Chen[8] demonstrated that similar high product diastereo- and enantioselectivities could be accomplished by employing the same metal catalyst with *N*-aminophthalimide as a nitrogen source.[9] In light of this work, we wondered whether the same nitrogen source and related *N*-amino compounds could be applied to a '$PhI(OAc)_2$ + RNH_2' mediated C=C bond aziridination procedure. Padwa et al. described that the iodosylbenzene mediated intramolecular aziridination of cyclic carbamates gave the corresponding products in good yields and selectivities.[4d] Herein, we describe the realization of a metal catalyst-free '$PhI(OAc)_2$ + RNH_2' (R = phthalimide, benzooxazolone) protocol for effecting intermolecular aziridination of a series of alkenes under mild conditions (Scheme 1).

The intermolecular aziridination of styrene was initially chosen as the substrate to establish the reaction conditions (Table 1). Treatment of styrene (1 equiv) with 1.5 equiv of $PhI(OAc)_2$, 1.4 equiv of *N*-aminophthalimide ($PthNH_2$) and 2.8 equiv of K_2CO_3, in CH_2Cl_2 at rt furnished aziridine **1a** in 85% yield (entry 1). Similar



Scheme 1. $PhI(OAc)_2$-mediated aziridination of a series of alkenes with N-substituted hydrazines.

* Corresponding author. Tel.: +852-2859-2154; fax: +852-2857-1586; e-mail: cmche@hku.hk

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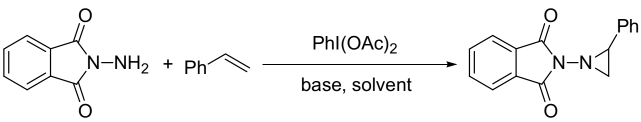
Table 1. Optimization of reaction conditions[a]



1a

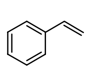
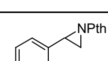
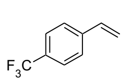
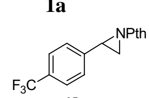
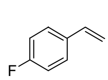
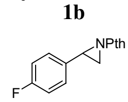
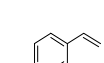
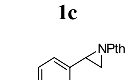
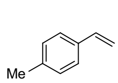
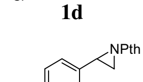
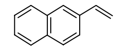
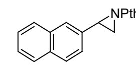
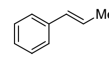
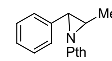
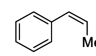
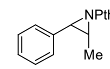
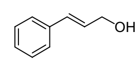
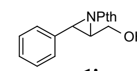
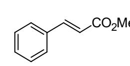
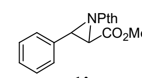
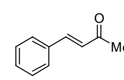
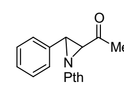
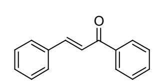
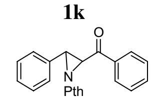
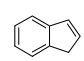
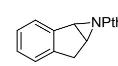
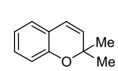
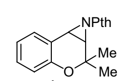
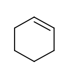
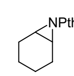
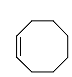
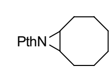
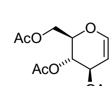
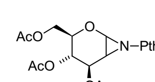
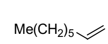
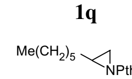
Entry	Solvent	Base	Temperature (°C)	Yield (%)[b]
1	CH_2Cl_2	K_2CO_3	rt	85
2	CH_2Cl_2	K_2CO_3	$0 \rightarrow$ rt	85
3	CH_2Cl_2	K_2CO_3	40	79
4	CH_2Cl_2	2,6-Cl_2py	rt	54
5	CH_2Cl_2	Al_2O_3	rt	13
6	CH_2Cl_2	KOH	rt	50
7	CH_2Cl_2	—	rt	71
8	C_6H_6	—	rt	76
9	THF	—	rt	50
10	MeCN	—	rt	59

[a] All reactions were performed for 12 h with styrene:$PhI(OAc)_2$:*N*-aminophthalimide:base molar ratio of 1:1.5:1.4:2.8.
[b] Isolated yield.

yields were obtained when the reaction was conducted at either 0 °C or at reflux (entries 2 and 3). In contrast, reactions employing either 2,6-dichloropyridine (2,6-Cl_2py), Al_2O_3 or KOH as the base gave significantly lower yields (entries 4–6). When base was removed from the reaction conditions, aziridine **1a** was afforded in a slightly lower yield (entry 7). An examination of solvent effects under these latter conditions revealed that a similar product yield was obtained when C_6H_6 was employed as the solvent (entry 8). The analogous reactions conducted in THF and acetonitrile, however, were found to give **1a** with markedly lower yields (entries 9 and 10).

In turning attention to exploring the generality of the present procedure, we examined the $PhI(OAc)_2$ mediated aziridination of a series of terminal and internal alkenes (Table 2). These reactions afforded the corresponding aziridines **1b**–**r** in good to excellent yields (up to 99%) and conversions (entries 2–18). In a number of cases product yields and conversions obtained were near quantitative (entries 1, 4, 5 and 10–12). More notably, the electron-rich and electron-deficient nature of the C=C bond was found to have no effect on reaction yield. A competitive rate study of a number of *para*-

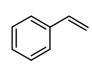
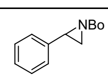
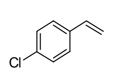
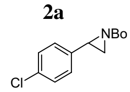
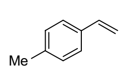
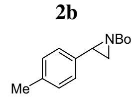
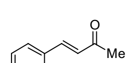
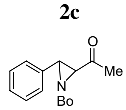
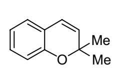
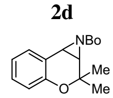
Table 2. Intermolecular $PhI(OAc)_2$-mediated aziridination with *N*-aminophthalimide[a]

Entry	Substrate	Product **1**	Conversion (%)	Yield (%)[b]
1		 **1a**	97	87
2		 **1b**	64	97
3		 **1c**	64	87
4		 **1d**	96	76
5		 **1e**	94	74
6		 **1f**	87	63
7		 **1g**	79	45
8		 **1h**	94	73
9		 **1i**	40	79
10		 **1j**	100	99
11		 **1k**	99	98
12		 **1l**	94	99
13		 **1m**	46	90
14		 **1n**	71	99
15		 **1o**	81	71
16		 **1p**	74	80
17		 **1q**	38	93[c]
18		 **1r**	29	77

[a] All reactions were performed for 12 h with alkene:$PhI(OAc)_2$:*N*-aminophthalimide:K_2CO_3 molar ratio of 1:1.5:1.4:2.8 in CH_2Cl_2 at rt.
[b] Isolated yield.
[c] Combined yield with a α:β ratio of = 1.5:1.

substituted styrenes (Y-$C_6H_4CH{=}CH_2$ where Y = Me, OMe, F, CF_3) did imply electron-deficient alkenes accelerated aziridination more quickly than electron-rich alkenes.[10] Furthermore, reaction of *cis*- and *trans*-β-methylstyrene giving **1g** and **1h** with exclusive *cis*- and *trans*-selectivity, respectively, suggests the present protocol to be diastereoselective (entries 7 and 8). In instances where it was initially envisaged that the presence of other functional groups would lead to competitive side reactions, the exclusive formation of the aziridine product implies the present procedure to be chemoselective. No other products that could be attributed to side reactions of the functional groups present in the alkenes examined were detected (entries 9–12). Conformationally restricted alkenes were found to undergo intermolecular aziridination. Aziridines **1m–q** were afforded in 80–99% yields based on conversions of 38–81% (entries 13–17). Reaction of 1-heptene is the only example where conversion was found to be moderate (entry 18). Nevertheless, in every instance lower product yields were reported for the analogous reactions catalyzed by LTA.[10,11] For example, the LTA-catalyzed aziridination of styrene with *N*-aminophthalimide gave **1a** in 42% yield in contrast to the 87% yield using the present procedure (Table 2, entry 1).[10] Furthermore, the present protocol realized aziridination of a broad spectrum of alkenes with $PhI(OAc)_2$ which is less toxic and more environmentally friendly than LTA.[12] This is exemplified by the aziridination of tri-*O*-acetyl-D-glucal in 93% yield based on 38% conversion and with an α:β ratio of 1.5:1 (entry 17). The analogous reaction with LTA is not known.

Table 3. Intermolecular $PhI(OAc)_2$-mediated aziridination with 3-amino-3*H*-benzooxazol-2-one as the nitrogen source[a]

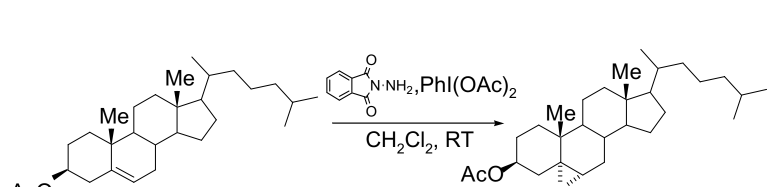
Entry	Substrate	Product **2**	Conversion (%)	Yield (%)[b]
1		 **2a**	53	80
2		 **2b**	54	84
3		 **2c**	55	82
4		 **2d**	42	94
5[c]		 **2e**	31	68

[a] All reactions were performed for 12 h with alkene:$PhI(OAc)_2$:3-amino-3*H*-benzooxazol-2-one:K_2CO_3 molar ratio of 1:1.5:1.4:2.8 in CH_2Cl_2 at rt.
[b] Isolated yield.
[c] Reaction conducted with 3 equiv of $PhI(OAc)_2$.

With 3-amino-3*H*-benzooxazol-2-one ($BoNH_2$) as a nitrogen source, the aziridination of a variety of alkenes proceeded in good to excellent yields and moderate to good conversions (Table 3). Treatment of styrene (1 equiv) with 1.5 equiv of $PhI(OAc)_2$, 1.4 equiv of 1-amino-1,3-dihydro-indol-2-one and 2.8 equiv of K_2CO_3, in CH_2Cl_2 at rt furnished aziridine **2a** in 53% yield (entry 1). Under similar conditions, yields up to 94% were obtained for the aziridination of both electron-deficient and -rich alkenes (entries 2–4). Likewise, reaction of 2,2-dimethyl-2*H*-chromene gave the corresponding aziridine product **2e** in 68% yield based on 31% conversion (entry 5).

Amino steroids have been shown to exhibit noteworthy pharmacological activity.[13] Previous work by Dauban and Dodd reported a copper catalyzed aziridination of 11-pregnene-3,20-dione in 53% yield.[14] Breslow demonstrated manganese porphyrin catalyzed amidation of equilenin acetate in 47% yield.[15] Work previously undertaken in our laboratory had shown that the amidation of cholesteryl acetate catalyzed by ruthenium porphyrin occurred with α-selectivity (α:β ratio up to 4.2:1),[3b] but the same reaction catalyzed by ruthenium–salen complexes resulted in β-selectivity (β:α ratio up to 2.3:1).[3c] It therefore intrigued us to explore the present $PhI(OAc)_2$-mediated aziridination protocol as an alternative route to these biologically interesting compounds. Thus, when cholesteryl acetate was treated in the presence of 1.5 equiv of $PhI(OAc)_2$, 1.4 equiv *N*-aminophthalimide and 2.8 equiv K_2CO_3 in CH_2Cl_2, aziridine **1t** was obtained in 95% isolated yield based on 29% conversion. By comparing the ^1H NMR spectrum obtained for **1t** with known literature data,[16] reaction was observed to occur with exclusive α-selectivity (Scheme 2). It is noteworthy that this is comparable to the product yield of 40% reported for the analogous reaction using LTA as the catalyst.[16]

In this Letter, we describe a practical and simple $PhI(OAc)_2$ mediated aziridination reaction that is both general and high yielding. Effects are currently underway to develop an asymmetric polyvalent iodine-mediated version of the present reaction and its application to the total synthesis of a variety of natural products.



1t
29% conversion, 95% yield

Scheme 2. $PhI(OAc)_2$-mediated aziridination of cholesteryl acetate.

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