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N-Amino-*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimide as an Active Aminoaziridinating Agent

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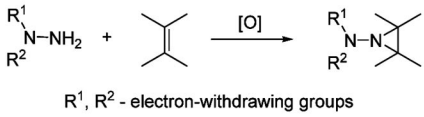
Dedicated to Prof. Armin de Meijere on the occasion of his 70th birthday

Keywords: Nitrogen heterocycles / Amines / Alkenes / Synthons

N-Amino-*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimide is active in the oxidative aminoaziridination reaction toward alkenes substituted with aryl-, alkyl, and electron-withdrawing groups, providing access to stable derivatives of *N*-aminoaziridine. Yields varied from 19 to 76 %, and *trans*-substituted alkenes reacted faster and gave better yields than *cis*-alkenes. No products of self-aziridination were isolated.

Introduction

Aminoaziridines are important synthons in organic synthesis capable of undergoing ring opening by nucleophiles.[1] They also serve as important precursors for α-hydrazino acids, which naturally occur in peptide antibiotics, the inhibit amino acid utilizing enzymes, and they can be used as metabolically stable peptide mimetics with antiviral potential.[2] Oxidative aminoaziridination is a direct and convenient way to access a wide range of stable derivatives of *N*-aminoaziridine (Scheme 1). A variety of *N*-aminoheterocycles were tested in this reaction[3] during the last several decades. However, only *N*-aminophthalimide[3a,4a–4d] and 3-aminoquinazolin-4(3*H*)-ones[3a,4e–4g] have found wide use.



Scheme 1. Oxidative aminoaziridination of alkenes.

Aminonitrene or a nitrene-type intermediate is considered to be the key intermediate when $Pb(OAc)_4$ is used as the oxidant.[3,4] Recently, we showed that *N*-amino-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide (EnN-NH_2, **1**) and $Pb(OAc)_4$ together form a good aziridinating system despite the presence of a norbornene-type carbon–carbon double bond in its structure[3j] (Figure 1). Herein, we report the structurally similar *N*-amino-*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimide (EPTN-NH_2, **2**), which possesses an *exo* configuration and which is also capable of oxidative aziridination of double bonds. Our findings suggest the involvement of a possibly different intermediate species for the EPTN-NH_2/$PhI(OAc)_2$ system. Apart from its synthetic utility, EPTN-NH_2 is also a compound of interest as a result of its structural similarity to cantharidine (**3**), a drug known for its antiviral and anticancer activity.[5]

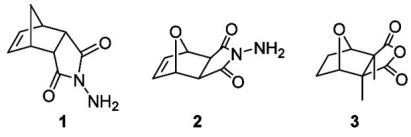


Figure 1. Structures of EnN-NH_2 (**1**), EPTN-NH_2 (**2**), and cantharidine (**3**).

The first synthesis of compound **2** was reported in 1965 by Furdik and Sidoova.[6a] In the early 1970s Augustin and Reinemann along with Title also published the synthesis of EPTN-NH_2 and its derivatives.[6b–6d] Between 1980 and 1990, several reports were published on the synthesis and biological activity of EPTN-NH_2 and related compounds,[5c,7] indicating their high uptake in lungs, kidneys, and spleen.[5b] Recently, Struga et al. reported the X-ray structure of EPTN-NH_2,[8] affirming its *exo* configuration.

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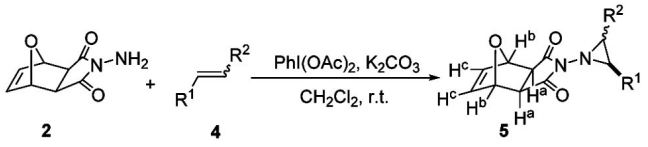
Results and Discussion

To our best knowledge, the oxidation of **2** in the presence of unsaturated compounds has not been investigated. For this study we chose a series of aryl- and alkyl-substituted alkenes, with either electron-donating or electron-withdrawing groups at the double bond, including cyclic compounds. Unless otherwise mentioned, most of the reactions were carried out with (diacetoxyiodo)benzene (1 equiv.) as the oxidant and unsaturated substrates **4** (1–3 equiv.) in dichloromethane solution at ambient temperature for 16 h. An excess amount of anhydrous potassium carbonate (3–4 equiv.) was used as a base (Scheme 2).



2 **4** **5**

Scheme 2. Oxidative aminoaziridination of alkenes with EPTN-NH_2/PhI$(OAc)_2$ system.

Most of the alkenes were converted into the corresponding aminoaziridines in yields varying from 19 to 76% (Table 1), but the reactivity of nonconjugated terminal alkenes varied from very low with hex-5-en-2-one – trace amounts of the product – to no reaction at all in the case of 4-phenylbut-1-ene. The use of an excess amount of alkenes **4a**, **4f**, **4m**, **4q**, and **4s** (see Table 1) did not provide better yields. In analogy with epoxidation, the oxidative aminoaziridination with **2** proceeded with retention of configuration of the alkene, which was confirmed by NMR spectroscopic analysis of compounds **5** and by X-ray structural data for compounds **5c** and **5f** (Figure 2). Configuration retention has been reported for other *N*-aminoaziridination protocols.[4g,9] All the aziridines shown in Table 1 are new compounds. Their compositions were confirmed by HRMS data and their structures by ^1H and ^{13}C NMR spectroscopy.

Despite the fact that **2** possesses a norbornene-type double bond, which is generally considered more reactive than an unstrained *cis* double bond, the product of intermolecular self-aziridination was never isolated from the reaction mixture. Also, a sharp variation in the yields was observed for *cis* and *trans* alkenes. For instance, aziridine **5g** from *trans*-stilbene was obtained in 76% yield, whereas *cis*-stilbene gave only 19% yield of **5h**. Similar results were obtained for dimethyl fumarate (**4e**; adduct **5e**, 56%) and dimethyl maleate (**4f**; adduct **5f**, 20%). Furthermore, we recorded low yields for cyclohexene (**4m**; adduct **5m**, 25%), cyclohexenone (**4p**; adduct **5p**, 21%), and naphthoquinone (**4n**; adduct **5n**, 21%). Although cyclohexenone did not give a good yield with the EnN-NH_2/Pb$(OAc)_4$ system, cyclohexene and naphthoquinone gave better results.[3j] Therefore, the observed low reactivity of the double bond of EPTN-NH_2 in the reaction could be due to the general low reactivity of *cis* double bonds with the reagent under the reaction conditions.

Table 1. Oxidative aminoaziridination of alkenes with EPTN-NH_2.[a]

Entry	Alkene	Alkene [equiv.]	Aziridine	Yield [%]
1	**4a**	1. 3	**5a**	54
2	**4b**	2	**5b**	58
3	**4c**	2	**5c**	51
4	**4d**	1	**5d**	40
5	**4e**	1	**5e**	56
6	**4f**	1. 3	**5f**	20
7	**4g**	1	**5g**	76
8	**4h**	1	**5h**	19
9	**4i**	1	**5i**	74
10	**4j**	1	**5j**	70
11	**4k**	1	**5k**	69
12	**4l**	1	**5l**	74
13	**4m**	1. 5	**5m**	25
14	**4n**	1	**5n**	21
15	**4o**	1	**5o**	30
16	**4p**	3	**5p**	21
17	**4q**	1. 3	**5q**	41
18	**4r**	3	—	—
19	**4s**	1. 3	**6**	40

[a] Yields are based on complete conversion of **2**.

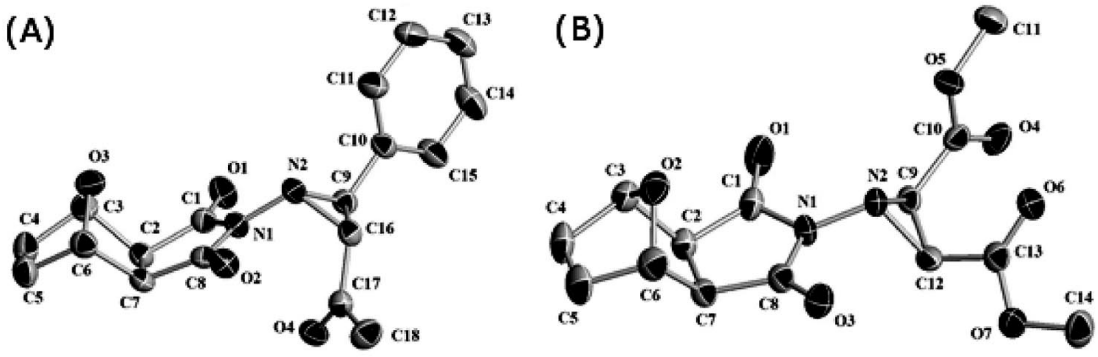
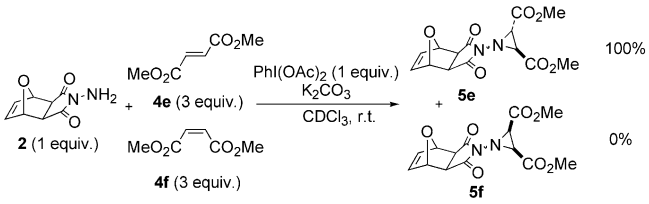


Figure 2. ORTEP renderings of the X-ray structures of compounds **5c** (A) and **5f** (B).

To elucidate our observations, we carried out a simple experiment to determine whether the low yields for *cis*-substituted alkenes were due to their low reactivity and not caused by slow crystallization rates of the corresponding aziridines, their instability under the reaction conditions, or any other factor. In this study *trans*- (**4e**) and *cis*-alkenes (**4f**) were taken in excess to **2** and diacetoxyiodobenzene [3 equiv. of each alkene to 1 equiv. of EPTN-NH_2 and 1 equiv. of $PhI(OAc)_2$] in $CDCl_3$ (Scheme 3). Reaction progress was monitored by ^1H NMR spectroscopy (Figure 3). Formation of *trans*-aziridine **5e** was expected to be observed by the appearance of the aziridine proton peak at 3.53 ppm, whereas the protons of *cis*-aziridine **5f** have a chemical shift of 3.46 ppm.



Scheme 3. Competitive addition of EPTN-NH_2 to dimethyl fumarate versus dimethyl maleate.

After 4 h at 21 °C the reaction was complete (with no compound **2** left, Figure 3). Interestingly, no compound **5f** was formed in this experiment. These results indicate that *trans*-alkene **4e** is much more reactive than its *cis*-isomer **4f** under the conditions described above.

We propose the involvement of a sterically demanding phenyliodo group in the transition state in agreement with a higher activation barrier for the *cis* alkene (Scheme 4). Richardson and co-workers suggested that a similar reaction with the *N*-aminophthalimide/$PhI(OAc)_2$ system can proceed not only via an aminonitrene or *N*-acetoxy derivative, but via an *N*-phenyliodo intermediate as well.[4g] In order to explain the difference in reactivity between *cis*- and *trans*-alkenes, one needs to compare the corresponding transition states. If the reactive species is a nitrene or nitrenoid (*N*-acetoxy derivative), no significant difference in steric interactions in the generalized transition state can be anticipated (Path A, Scheme 4) to explain the difference in reactivity of *cis* and *trans* alkenes. Unfavorable interaction between R^1 and R^2 in case of the *cis* alkene is outweighed by the *trans* orientation of the EPTN substituent. Similarly, in the case of the *trans* alkene, an unfavorable interaction between R^1 (or R^2) and EPTN is offset by the *trans* configuration of R^1 and R^2. If the reactive species is an adduct of EPTN-NH_2 and $PhI(OAc)_2$ (Paths B and C, Scheme 4), a significant steric demand is predicted on the transition state

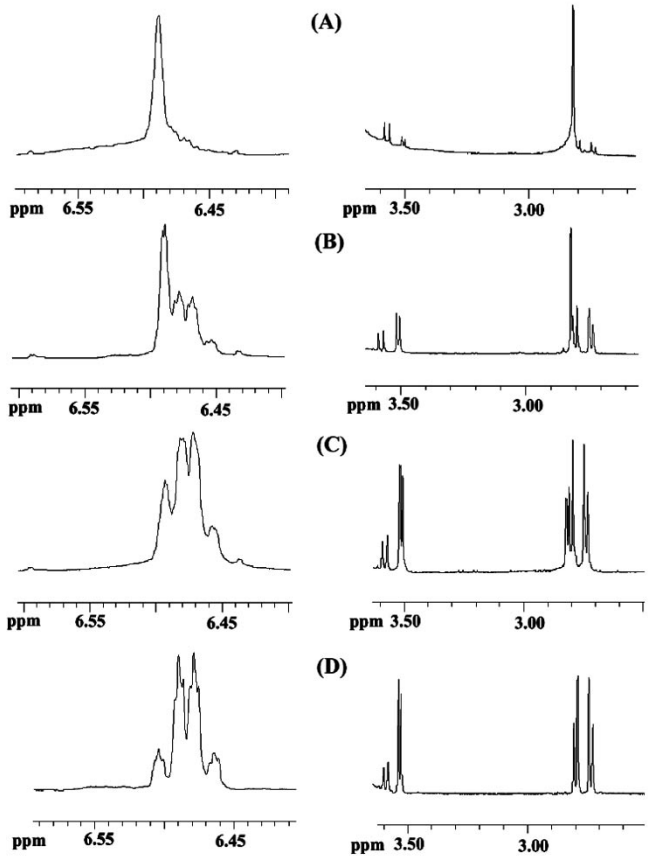
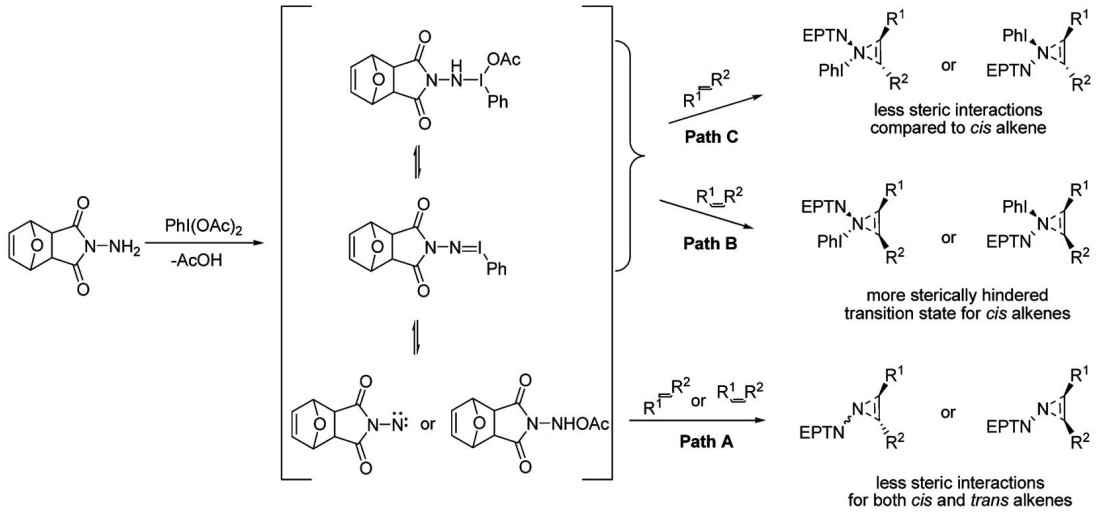


Figure 3. ^1H NMR spectroscopic study of competitive oxidative addition of EPTN-NH_2 to dimethyl fumarate (**4e**) versus dimethyl maleate (**4f**) in $CDCl_3$. Expansions shown: 6.6–6.4 ppm (H^c peak of **2** disappears, H^c and $H^{c'}$ peaks of **5e** appear) and 3.6–2.5 ppm (H^a peak of **2** disappears, H^a, $H^{a'}$ and H^{az} peaks of **5e** appear). (A) 5 min, 2% conv., (B) 62 min, 21% conv., (C) 176 min, 74% conv., (D) 270 min., 100% conv.



Scheme 4. Proposed mechanisms for oxidative aminoaziridination with the EPTN-NH_2/$PhI(OAc)_2$ system.

involving the *cis* alkene compared with that of the *trans* alkene. EPTN as well as phenyliodo groups are bulky, and the presence of both of them in the transition state accounts for the additional increment in total energy of this particular transition state. For example, in the case of *cis* alkene (Path B, Scheme 4) this energy increment for the transition state is the largest due to strong steric interactions between R^1, R^2 and either EPTN or PhI. In other words, three substituents crowd on one side of the ring, whereas there is only one substituent on the opposite side. To the contrary, in the transition state involving *trans* alkenes (Path C, Scheme 4), substituents are distributed evenly on both sides of the aziridine ring, which lowers the overall energy of the transition state. Such an energy difference may account for the higher activation barrier and, hence, slower rate of reaction and lower general reactivity of *cis* alkenes under these conditions. This explanation also questions the nitrene/nitrenoid mechanism for this particular substrate/oxidant pair.

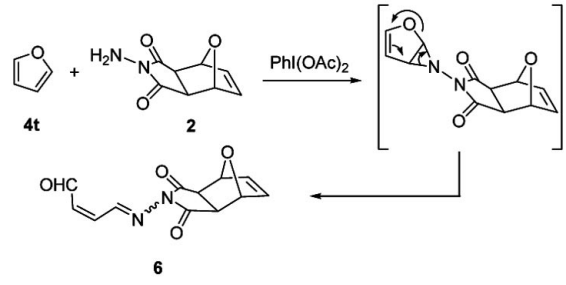
Generally, aminoaziridines are known to have a considerable barrier towards inversion of the endocyclic nitrogen atom, which usually leads to co-existence of the two invertomers on the NMR timescale. However, most products **5** showed only one set of signals in the ^1H NMR spectra, which indicates that one of the invertomers strongly prevails. This may be due to the bulkiness of the *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimide fragment, which prefers an *anti* position to the largest substituent in the aziridine ring. For molecules **5e** and **5g** with the axial symmetry of the aziridine fragment, nitrogen inversion is a degenerate process. However, the slow rate of inversion in these cases causes nonequivalence of the *syn* and *anti* substituents (as related to the EPTN group) at the carbon atoms of the aziridine ring. Similar behavior is observed in the case of aminoaziridine derivatives with an EnN group.[3j]

As expected, the NMR spectra pattern for the tricyclic fragment in compound **2** and in most aziridines **5** differs significantly. The value of $^3J_{a,b}$ in the ^1H NMR spectrum of starting heterocycle **2** is less than 2 Hz, which is in a good agreement with its *exo* configuration. Because the value of $^3J_{b,c}$ is also small, signals of pairwise enantiotopic H^a, H^b, and H^c atoms appear in the form of singlets with no visible spin–spin interaction. However, for the majority of compounds **5** (except for molecules **5f**, **5h**, **5m**, and **5n** with a symmetry plane) the chirality of the aziridine fragment causes the diastereotopicity of initially enantiotopic atoms and groups in the tricyclic moiety. This leads to the doubling of the corresponding signals in the NMR spectra and to the visible appearance of spin–spin interaction between these nuclei (we observe AB or even AX spin systems instead of A_2). Therefore, this interaction depends on the distance between the centers of chirality and the atom or group under consideration.

When other dynamic processes, such as rotation around the N–N bond in some sterically hindered compounds **5**, are slowed down, additional complications in the NMR spectra are observed. This could be the reason why there are broad H^a and H^b signals along with sharp $H^{a'}$ and $H^{b'}$ peaks (see Scheme 2) in the spectrum of *trans*-stilbene adduct **5g**. It is possible that the chemical shifts for one of the atoms of the diastereomeric pair do not differ significantly in both rotamers (the signal appears sharp). In the ^1H NMR spectra of chiral aziridines **5**, spin–spin interactions can be observed between diastereotopic H^a and $H^{a'}$ atoms ($^3J_{a,a'}$ = 6.4 Hz) and in some cases between the H^c and $H^{c'}$ atoms ($^3J_{c,c'}$ = 5.6–6.0 Hz) of the tricyclic fragments. The degree of nonequivalence (chemical shifts difference) can vary from case to case. At the same time, another atom of that pair can have rather different chemical shifts for these rotamers, which results in a broader peak at the same rotation rate. In the ^{13}C NMR spectrum of adduct **5g** the peak of a carbon atom in the aziridine moiety at 53.8 ppm is sharp, but the second one at 45.3 ppm is broadened, which is likely to be caused by the same reason. In contrast, the spectra of less sterically hindered fumarate derivative **5e** shows sharp peaks for all protons and carbon atoms men-

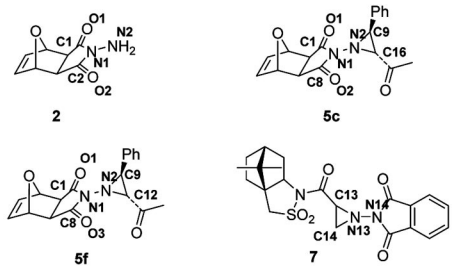
tioned above. More complicated are the NMR spectra of adduct with β-nitrostyrene **5o**. For this compound, we observed two invertomers in a ratio of about 2:1, as well as the slow rotation around the N–N bond (same for compound **5g**), which causes significant broadening of many signals in the ^{1}H and ^{13}C NMR spectra. Unexpectedly, neither low- (–20 and –50 °C) nor high-temperature (+50 °C) NMR spectroscopic investigations helped to clarify the ^{1}H spectrum of **5o**. At elevated temperature all peaks broadened further, which indicated that at 50 °C many signals of compound **5o** are approaching their coalescence temperatures for nitrogen inversion. At low temperatures, we observed that some of the peaks broadened. This may be due to a decrease in the rate of rotation around the N–N bond. All these effects significantly complicated the peak assignments, which we were able to do only partially.

No significant difference in yields was observed among the chalcone series between adducts with electron-donating and electron-withdrawing substituents in the *para* position of the phenyl ring (compounds **4i**–**l**). However, aminoaziridines formed from alkenes with electron-donating substituents attached directly to the double bond are generally known to be unstable.[10] The structures of their decomposition products depend on the nature of the substituents in the alkene.[3a] In our attempt to react **2** with isobutyl vinyl ether (**4r**), the corresponding aziridine was not isolated. When furan (3 equiv.) was used as a trap instead of an alkene, previously unknown aldehyde **6** was isolated in 40% yield. Formation of **6** could be explained by initial addition of **2** to the carbon–carbon double bond of furan followed by ring opening (Scheme 5). The *cis* configuration of aldehyde **6** was deduced from the small value of the vicinal spin–spin constant between the olefinic protons (10 Hz), which is in good agreement with the proposed formation mechanism (Scheme 5) and the reported literature data.[10] It is interesting to note that the oxidative aminoaziridination of furan in the most often used *N*-aminophthalimide/$Pb(OAc)_4$ system produced an intractable product.[10a]



Scheme 5. Oxidative addition of EPTN-NH_2 to furan.

Comparing the crystal structures of compounds **5c** and **5f** (Figure 4) with the crystal structures of starting heterocycle **2** and *N*-phthalimidoaziridine **7** revealed no significant difference in N–N bond lengths: 1.418, 1.420, 1.418, and 1.425 Å. The bond lengths in the aziridine cycle vary within 0.005 Å for compounds **5c** and **5f**. However, the aziridine carbon–nitrogen and carbon–carbon bonds are somewhat shorter for phthalimide derivative **7**.[2b,8] A noticeable structural feature of both adducts **5** is the *trans* orientation of the aziridine ring and the tricyclic fragment. NMR spectroscopic data also suggests that compound **5c** exists as a *trans* isomer/*anti* invertomer (*cis* isomer/*anti* invertomer for **5f**), which was confirmed by X-ray studies.



Bond Lenghts [Å]

2		5c		5f		7	
N1-C1	1.364(6)	N1-C1	1.3847	N1-C1	1.395(3)		
N1-C2	1.381(5)	N1-C8	1.3905	N1-C8	1.402(3)		
C1-O1	1.225(5)	C1-O1	1.2075	C1-O1	1.203(3)		
C2-O2	1.221(5)	C8-O2	1.2082	C8-O3	1.213(3)		
N1-N2	1.418(5)	N1-N2	1.4184	N1-N2	1.420(3)	N13-N14	1.425(8)
		C9-N2	1.4707	C9-N2	1.475(3)	C14-N13	1.460(13)
		C16-N2	1.506(2)	C12-N2	1.503(3)	C13-N13	1.484(11)
		C9-C16	1.488(2)	C9-C12	1.493(3)	C13-C14	1.462(16)

Figure 4. Bond lengths in compounds **2**, **5c**, **5f**, and **7**.

Conclusions

N-Amino-*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimide is an active aminoaziridinating agent that reacts with alkenes containing a variety of substituents. Despite possessing its own double bond, no evidence of self-aziridination was found. A number of novel derivatives of *N*-aminoaziridine were obtained in yields of 19–76%, and these derivatives were characterized by NMR spectroscopy, HRMS, and single-crystal X-ray diffraction (compounds **5c** and **5f**). A competitive study of the reactivity of *cis* versus *trans* alkenes demonstrates strong selectivity towards the *trans* alkene. Our results question the "nitrene"-based mechanism when phenyliodobenzene is used as an oxidant.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with a 400 MHz spectrometer in $CDCl_3$ by using tetramethylsilane (δ = 0.00 ppm) as an internal standard for ^{1}H NMR and $CDCl_3$ (δ = 77.0 ppm) as an internal standard for ^{13}C NMR spectroscopy. High-resolution mass spectra (ESI or FAB) were obtained with a Fourier transform mass spectrometer. Reactions were monitored by thin-layer chromatography carried out on F^{254} silica gel coated plates by using UV visualization and basic $KMnO_4$ solution as a developing agent. All reagents and solvents were commercially available and were used as supplied without additional purification.

***N*-Amino-*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimide (2):**[6] Hydrazine hydrate (18 g, 0.36 mol, 1.2 equiv.) was added to *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (50.0 g, 0.30 mol) in isopropyl alcohol (300 mL). The mixture was heated at reflux for 3 h and then cooled down to 0 °C. The yellowish crystalline precipitate of **2** was smashed into pieces, filtered off, recrystallized from

MeOH, and then dried in the air. Yield: 32.3 g (60%). M.p. 186–187 °C (ref.[6a] 187–188 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83 (s, 1 H, H^a), 4.27 (s, 2 H, NH_2), 5.26 (s, 2 H, H^b), 6.51 (s, 2 H, H^c) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.5 (C-1,2), 80.5 (C-3,6), 136.3 (C-4,5), 173.6 (C=O) ppm. HRMS (ESI+): calcd. for $C_8H_8N_2O_3$ [M + H]$^+$ 181.0613; found 181.0613 (–0.1 ppm error).

General Procedure for the Preparation of Compounds 5 and 6: Anhydrous K_2CO_3 (3.1 g, 22.5 mmol), $PhI(OAc)_2$ (1.8 g, 5.6 mmol), **2** (1.0 g, 5.6 mmol), and the alkene (1–5 equiv.) were mixed and then CH_2Cl_2 (30 mL) was added. The mixture was stirred at room temperature for 16 h. The resulting suspension was centrifuged, and after washing the precipitate with CH_2Cl_2 (30 mL) the combined supernatant was filtered through a short plug of silica gel. The solvent was removed under reduced pressure without heating, and the residue was triturated with diethyl ether (15 mL). If no crystallization occurred, the crude product was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:1). Recrystallization of the product from methanol was necessary in some cases.

1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-2-phenylaziridine (5a): Yield: 854 mg (54%). White crystals, m.p. 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67–2.72 (m, 2 H, H^{cis} + H^{trans}), 2.77 (s, 2 H, H^a + $H^{a'}$), 3.44 (dd, J = 7.6, 6.0 Hz, 1 H, CHPh), 5.25 (s, 1 H, H^b), 5.27 (s, 1 H, $H^{b'}$), 6.50 (s, 2 H, H^c + $H^{c'}$), 7.29–7.41 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.00 (CH_2), 44.60 (NCH), 45.54 (C-1,2), 80.60 and 80.61 (C-3,6), 127.03, 128.03 (C^p), 128.49, 136.22 (C^i), 136.33 and 136.37 (C-4,5), 172.21 (NC=O) ppm. HRMS (ESI+): calcd. for $C_{16}H_{14}N_2O_3$ [M + H]$^+$ 283.1077; found 283.1077 (–0.1 ppm error).

Methyl 1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-phenylaziridine-2-carboxylate (5b): Yield: 1.105 g (58%). White crystals, m.p. 161–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.77 (d, J = 6.4 Hz, 1 H, H^a), 2.83 (d, J = 6.4 Hz, 1 H, $H^{a'}$), 3.43 (d, J = 4.8 Hz, 1 H, *CH*CO_2Me), 3.75 (s, 3 H, MeO), 4.13 (d, J = 4.8 Hz, 1 H, C*H*Ph), 5.25 (s, 1 H, H^b), 5.29 (s, 1 H, $H^{b'}$), 6.49 (m, 2 H, H^c + $H^{c'}$), 7.30–7.42 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.33, 45.83 (2 C), 49.32, 52.84 (MeO), 80.36 and 80.51 (C-3 and C-6), 127.03 (C^o or C^m) 128.58 (C^m or C^o + C^p), 134.24 (C^i), 136.26 and 136.46 (C-4 and C-5), 166.57 (*C*O_2Me), 171.94 and 172.24 (2 NC=O) ppm. HRMS (ESI+): calcd. for $C_{18}H_{16}N_2O_5$ [M + H]$^+$ 341.1132; found 341.1132 (–0.4 ppm error).

2-Acetyl-1-(*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-phenylaziridine (5c): Yield: 1.003 g (51%). White crystals, m.p. 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CO*Me*), 2.69 (d, J = 6.4 Hz, 1 H, H^a), 2.83 (d, J = 6.4 Hz, 1 H, $H^{a'}$), 3.60 (d, J = 4.8 Hz, 1 H, *CH*Ac), 4.11 (d, J = 4.8 Hz, 1 H, *CH*Ph), 5.25 (s, 1 H, H^b), 5.26 (s, 1 H, $H^{b'}$), 6.48 (m, 2 H, H^c + $H^{c'}$), 7.30–7.40 (m, 5 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.29 (Me), 45.30 and 45.79 (C-1 and C-2), 49.64 (N*CH*Ph), 50.86 (N*CH*Ac), 80.30 and 80.51 (C-3 and C-6), 126.91, 128.52 (C^p), 128.59, 134.72 (C^i), 136.26 and 136.43 (C-4 and C-5), 172.02 and 172.33 (2 NC=O), 198.24 (C=O) ppm. HRMS (ESI+): calcd. for $C_{18}H_{16}N_2O_4$ [M + H]$^+$ 325.1183; found 325.1183 (–0.3 ppm error).

2-Acetyl-1-(*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-(4-methoxyphenyl)aziridine (5d): Yield: 793 mg (40%). White crystals, m.p. 151–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, *Me*CO), 2.70 (d, J = 6.4 Hz, 1 H, H^a), 2.83 (d, J = 6.4 Hz, 1 H, $H^{a'}$), 3.59 (d, J = 4.4 Hz, 1 H, *CH*Ac), 3.80 (s, 3 H, O*Me*), 4.06 (d, J = 4.4 Hz, 1 H, Ar*CH*), 5.25 (s, 1 H, H^b), 5.26 (s, 1 H, $H^{b'}$), 6.49 (m, 2 H, H^c + $H^{c'}$), 6.89 (m, 2 H, H^m), 7.30 (m, 2 H, H^o) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.31 (CO*Me*), 45.30 and 45.80 (C-1 and C-2), 49.53 (N*CH*Ph), 50.78 (N*CH*Ac), 55.31 (MeO), 80.30 and 80.52 (C-3,6), 114.07 (C^m), 128.18 (C^o), 130.82 (C^i), 136.26 and 136.44 (C-4,5), 159.83 (*C*-OMe), 172.08 (NC=O), 172.38 (NC=O), 198.41 (C=O) ppm. HRMS (ESI+): calcd. for $C_{19}H_{18}N_2O_5$ [M + H]$^+$ 355.1288; found 355.1286 (–0.2 ppm error).

Dimethyl 1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)aziridine-*trans*-2,3-dicarboxylate (5e): Yield: 1.001 g (56%). White crystals, m.p. 156–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.73 (d, J = 6.4 Hz, 1 H, H^a), 2.80 (d, J = 6.4 Hz, 1 H, $H^{a'}$), 3.53 (d, J = 4.4 Hz, 1 H, NCH), 3.72 (d, 1 H, NCH), 3.73 (s, 3 H, MeO), 3.82 (s, 3 H, MeO), 5.22 (s, 1 H, H^b), 5.24 (s, 1 H, $H^{b'}$), 6.48 (m, 2 H, H^c + $H^{c'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.44, 44.35, 45.37, 45.78, 53.13 (MeO), 53.22 (MeO), 80.35 and 80.52 (C-3 and C-6), 136.31 and 136.49 (C-4 and C-5), 165.15 (*C*O_2Me), 166.35 (*C*O_2Me), 171.43 (NC=O), 171.57 (NC=O) ppm. HRMS (ESI+): calcd. for $C_{14}H_{14}N_2O_7$ [M + Na]$^+$ 345.0693; found 345.0693 (–0.3 ppm error).

Dimethyl 1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)aziridine-*cis*-2,3-dicarboxylate (5f): Yield: 361 mg (20%). White crystals, m.p. 168–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79 (s, 2 H, H^a), 3.46 (s, 2 H, NCH), 3.83 (s, 6 H, MeO), 5.24 (s, 2 H, H^b), 6.50 (s, 2 H, H^c) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.06 and 45.58 (NCH and C-1,2), 53.11 (MeO), 80.61 (C-3,6), 136.38 (C-4,5), 165.25 (*C*O_2Me), 171.08 (NC=O) ppm. HRMS (ESI+): calcd. for $C_{14}H_{14}N_2O_7$ [M + Na]$^+$ 345.0693; found 345.0693 (–0.3 ppm error).

1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-*trans*-2,3-diphenylaziridine (5g): Yield: 1.525 g (76%). White crystals, m.p. 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 (br. s, 1 H, H^a), 2.57 (d, J = 6.8 Hz, 1 H, $H^{a'}$), 3.89 (d, J = 6.0 Hz, 1 H, NCH), 4.64 (d, J = 5.6 Hz, 1 H, NCH), 4.83 (br. s, 1 H, H^b), 5.17 (s, 1 H, $H^{b'}$), 6.39 (m, 2 H, H^c + $H^{c'}$), 7.27–7.42 (m, 8 H, Ph + $H^{m,p}$), 7.50 (m, 2 H, H^o) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.37 (br. s, NCH), 45.37 and 46.37 (C-1,2), 53.80 (NCH), 80.10 and 80.33 (C-3,6), 127.01, 127.98, 128.04 (C^p), 128.52, 128.68 (C^p), 129.47, 130.73 (C^i), 135.86 and 136.50 (C-4,5), 136.36 (C^i), 172.49 (NC=O), 172.79 (NC=O) ppm. HRMS (ESI+): calcd. for $C_{22}H_{18}N_2O_3$ [M + H]$^+$ 359.1396; found 359.1390 (–0.1 ppm error).

1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-*cis*-2,3-diphenylaziridine (5h): Yield: 381 mg (19%). White crystals, m.p. 195–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83 (s, 2 H, H^a), 3.93 (s, 2 H, NCH), 5.30 (m, 2 H, H^b), 6.53 (m, 2 H, H^c), 7.14–7.25 (m, 10 H, Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.68 (C-1,2), 51.85 (NCH), 80.67 (C-3,6), 127.41 (C^p), 127.89, 128.13, 133.31 (C^i), 136.39 (C-4,5), 172.10 (NC=O) ppm. HRMS (ESI+): calcd. for $C_{22}H_{18}N_2O_3$ [M + H]$^+$ 359.1390; found 359.1390 (–0.3 ppm error).

2-Benzoyl-1-(*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-phenylaziridine (5i): Yield: 1.601 g (74%). White crystals, m.p. 177–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (d, J = 6.4 Hz, 1 H, H^a), 2.87 (d, J = 6.4 Hz, 1 H, $H^{a'}$), 4.30 (d, J = 4.8 Hz, 1 H, NCH), 4.42 (d, J = 4.8 Hz, 1 H, NCH), 5.23 (d, J = 1.6 Hz, 1 H, H^b), 5.26 (d, J = 1.6 Hz, 1 H, $H^{b'}$), 6.45 (m, 1 H, H^c), 6.50 (m, 1 H, $H^{c'}$), 7.32–7.54 (m, 7 H, Ph + H^m), 7.58–7.64 (m, 1 H, H^p), 8.04–8.08 (m, 2 H, H^o) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.29 and 45.87 (C-1,2), 48.51 (NCH), 50.37 (NCH), 80.36 and 80.60 (C-3,6), 127.06, 128.56, 128.65, 128.72, 133.61 (C^p Bz), 134.97 (C^i Bz), 136.26 and 136.47 (C-4,5), 137.12 (C^i Ph), 172.04 (NC=O), 172.13 (NC=O), 190.16 (C=O) ppm. HRMS (ESI+): calcd. for $C_{23}H_{18}N_2O_4$ [M + H]$^+$ 387.1339; found 387.1339 (–0.7 ppm error).

2-Benzoyl-1-(*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-(4-nitrophenyl)aziridine (5j): Yield: 1.691 g (70%). White crystals, m.p.

171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.71 (d, J = 6.4 Hz, 1 H, H^a), 2.88 (d, J = 6.4 Hz, 1 H, H$^{a'}$), 4.29 (d, J = 4.4 Hz, 1 H, NCH), 4.48 (d, J = 4.4 Hz, 1 H, NCH), 5.24 (d, J = 1.6 Hz, 1 H, H^b), 5.26 (d, J = 1.6 Hz, 1 H, H$^{b'}$), 6.46 (m, 1 H, H^c), 6.50 (m, 1 H. H$^{c'}$), 7.50–7.56 (m, 2 H, H^m), 7.61–7.66 (m, 3 H, H$^{o'}$ + H^p), 8.04–8.09 (m, 2 H, H^o), 8.21–8.26 (m, 2 H, H$^{m'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.30 and 45.85 (C-1,2), 48.59 (NCH), 48.92 (NCH), 80.36 and 80.60 (C-3,6), 123.81 (*p*-$C_6H_4NO_2$, C^m), 128.05, 128.79, 128.80, 133.33 (Bz C^i), 133.91 (Bz C^p), 136.24 and 136.43 (C-4,5), 141.45 and 142.28 (*p*-$C_6H_4NO_2$, C^i and C^p), 171.87 (NC=O), 171.95 (NC=O), 189.15 (C=O) ppm. HRMS (ESI+): calcd. for $C_{23}H_{17}N_3O_6$ [M + Na]$^+$ 454.1010; found 454.1010 (–0.4 ppm error).

2-Benzoyl-1-(*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-(4-chlorophenyl)aziridine (5k): Yield: 1.626 g (69%). White crystals, m.p. 179–180 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (d, J = 6.4 Hz, 1 H, H^a), 2.86 (d, J = 6.4 Hz, 1 H, H$^{a'}$), 4.25 (d, J = 4.8 Hz, 1 H, NCH), 4.38 (d, J = 4.8 Hz, 1 H, NCH), 5.22 (d, J = 1.6 Hz, 1 H, H^b), 5.26 (d, J = 1.6 Hz, 1 H, H$^{b'}$), 6.45 (m, 1 H, H^c), 6.50 (m, 1 H, H$^{c'}$), 7.32–7.42 (m, 4 H, *p*-C_6H_4Cl), 7.49–7.54 (m, 2 H, H^m), 7.61 (m, 1 H, H^p), 8.04–8.08 (m, 2 H, H^o) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.30 and 45.87 (C-1,2), 48.45 (NCH), 49.56 (NCH), 80.36 and 80.61 (C-3,6), 128.75, 128.77, 128.85, 133.55 (Bz, C^i or *p*-ClC_6H_4, C-Cl), 133.72 (Bz C^p), 134.48 (Bz, C^i or *p*-ClC_6H_4, C-Cl), 136.27 and 136.46 (C-4,5), 136.99 (*p*-C_6H_4Cl, C^i), 172.02 (NC=O), 172.05 (NC=O), 189.85 (C=O) ppm. HRMS (ESI+): calcd. for $C_{23}H_{17}ClN_2O_4$ [M + H]$^+$ 421.0950; found 421.0950 (–0.7 ppm error).

2-Benzoyl-1-(*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-(4-methoxyphenyl)aziridine (5l): Yield: 1.726 g (74%). White crystals, m.p. 179–180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (d, J = 6.4 Hz, 1 H, H^a), 2.86 (d, J = 6.4 Hz, 1 H, H$^{a'}$), 3.81 (s, 3 H, O*Me*), 4.28 (d, J = 4.8 Hz, 1 H, NCH), 4.36 (d, J = 4.8 Hz, 1 H, NCH), 5.22 (d, J = 1 Hz, 1 H, H^b), 5.26 (d, J = 1 Hz, 1 H, H$^{b'}$), 6.44 (m, 1 H, H^c), 6.49 (m, 1 H, H$^{c'}$), 6.90 (m, 2 H, H^m), 7.38 (m, 2 H, H^o), 7.51 (m, 2 H, H^2 Bz), 7.61 (m, 1 H, H^3 Bz), 8.05 (m, 2 H, H^1 Bz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.27 and 45.86 (C-1,2), 48.43 (NCH), 50.24 (NCH), 55.35 (MeO), 80.34 and 80.58 (C-3,6), 114.11 (C^m), 126.97 (*p*-Anys, C^i), 128.32, 128.69, 128.71, 133.55 (Bz, C^p), 136.25 and 136.46 (C-4,5), 137.19 (Bz, C^i), 159.87 (*C*-OMe), 172.05 (NC=O), 172.14 (NC=O), 190.30 (C=O) ppm. HRMS (ESI+): calcd. for $C_{24}H_{20}N_2O_5$ [M + H]$^+$ 417.1445; found 417.1445 (–0.3 ppm error).

7-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-7-azabicyclo[4.1.0]-heptane (5m): Yield: 364 mg (25%). White crystals, m.p. 170–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.29 (m, 2 H), 1.32–1.44 (m, 2 H), 1.84–1.94 (m, 2 H), 2.12–2.22 (m, 2 H), 2.57 (m, 2 H, H$^{1'}$), 2.70 (s, 2 H, H^a), 5.20 (s, 2 H, H^b), 6.47 (s, 2 H, H^c) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.91 (C$^{3'}$), 23.02 (C$^{2'}$), 43.97 and 45.53 (C$^{1'}$ and C-1,2), 80.51 (C-3,6), 136.30 (C-4,5), 172.51 (NCO) ppm. HRMS (ESI+): calcd. for $C_{14}H_{16}N_2O_3$ [M + H]$^+$ 261.1234; found 261.1234 (+0.1 ppm error).

1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-1a,7a-dihydro-1*H*-naphtho[2,3-*b*]azirene-2,7-dione (5n): Yield: 395 mg (21%). Yellow crystals, m.p. 179–180 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.87 (s, 2 H, H^a), 3.91 (s, 2 H, H^{az}), 5.12 (s, 2 H, H^b), 6.53 (s, 2 H, H^c), 7.85–7.96 (m, 4 H, *o*-C_6H_4) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 45.26 (C-1,2), 48.76 (NCH), 80.23 (C-3,6), 126.35 (C-3,6, Ar), 132.64 (C-2a,6a, Ar), 134.70 (C-4,5, Ar), 136.28 (C-4,5), 171.83 (NC=O), 188.38 (C=O) ppm. HRMS (ESI+): calcd. for $C_{18}H_{12}N_2O_5$ [M + H]$^+$ 337.0819; found 337.0819 (–0.3 ppm error).

1-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-2-nitro-3-phenylaziridine (5o): Yield: 549 mg (30%). Light-yellow crystals, m.p. 133–134 °C (decomp.). Two invertomers ≈2:1.[4] ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.51–2.68 (br. m, 2 H, 1,2-H major), 2.77–2.95 (br. m, 1 H, 1,2-H minor), 4.51 (br. s, 1 H), 4.68–4.74 (br. m, 1.5 H), 5.15 (s, 1 H), 5.25–5.35 (br. m, 1 H), 5.43 (br. s, 0.5 H), 6.35–6.60 (br. m, 4 H, 4,5-H + *CH*NO_2 major), 7.25–7.48 (br. m, 8 H, Ph + *CH*NO_2 minor) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.30, 45.72 and 46.08 (minor) (C-1,2); 49.89 (N*CH*Ph minor), 51.70 (N*CH*Ph major), 70.95 (*CH*NO_2 major), 73.60 (*CH*NO_2 minor); 80.23 and 80.41 (C-3,6); 127.18, 128.65, 128.92, 129.50, 130.18; 135.92, 136.39 and 136.49 (C-4,5 and C^i) ppm. HRMS (ESI+): calcd. for $C_{16}H_{13}N_3O_5$ [M + H]$^+$ 328.0928; found 328.0928 (–0.4 ppm error).

7-(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)-7-azabicyclo[4.1.0]heptan-2-one (5p): Yield: 322 mg (21%). White crystals, m.p. 163–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.71 (m, 1 H), 1.83–2.12 (m, 3 H), 2.40–2.52 (m, 2 H), 2.75 (s, 2 H, H^a), 2.87 (d, J = 7.2 Hz, H$^{1'}$), 3.22 (dt, J = 7.2, 2.4 Hz, 1 H, H$^{6'}$), 5.21 (m, 2 H, H^b), 6.48 (m, 2 H, H^c) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.99 (C-4′), 21.84 (C-5′), 36.87 (C-3′), 45.44 and 45.50 (C-1,2), 46.25 (C-6′), 49.09 (C-1′), 80.57 and 80.61 (C-3,6), 136.29 (C-4,5), 171.75 (NC=O), 202.83 (C-2′) ppm. HRMS (ESI+): calcd. for $C_{14}H_{14}N_2O_4$ [M + H]$^+$ 275.1032; found 275.1032 (–0.7 ppm error).

2-Acetyl-1-(*exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalimidyl)-3-pentylaziridine (5q): Yield: 730 mg (41%). White crystals, m.p. 124–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (m, 3 H, Me of C_5H_{11}), 1.28–1.38 (m, 4 H), 1.48–1.58 (m, 3 H), 1.77 (m, 1 H), 2.43 (s, 3 H, COMe), 2.64 (d, J = 6.4 Hz, 1 H, H^a), 2.78 (d, J = 6.4 Hz, 1 H, H$^{a'}$), 3.14 (m, 1 H, NCHC$_5$H$_{11}$), 3.20 (d, J = 4.8 Hz, 1 H, NCHCOMe), 5.22 (s, 1 H, H^b), 5.25 (s, 1 H, H$^{b'}$), 6.47 (m, 2 H, H^c + H$^{c'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.99 (Me of C_5H_{11}), 22.45, 25.65, 26.94, 31.09, 31.50 (4CH$_2$ and Me of Ac), 45.17 and 45.81 (C-1,2), 48.62 (NCH), 49.35 (NCH), 80.29 and 80.50 (C-3,6), 136.29 and 136.39 (C-4,5), 172.24 (NC=O), 172.62 (NC=O), 199.37 (C=O) ppm. HRMS (ESI+): calcd. for $C_{17}H_{22}N_2O_4$ [M + H]$^+$ 319.1658; found 319.1658 (–0.3 ppm error).

(2*Z*)-4-[(*exo*-3,6-Epoxy-1,2,3,6-tetrahydrophthalimidyl)imino]but-2-enal (6): Yield: 551 mg (40%). Yellow crystals, decomposes below 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (s, 2 H, H^a), 5.36 (s, 2 H, H^b), 6.44 (ddd, J = 11.6, 6.8, 1.2 Hz, 1 H, H^1), 6.55 (s, 2 H, H^c), 7.09 (dd, J = 11.6, 10.0 Hz, 1 H, H^2), 10.07 (dd, J = 10.0, 1.2 Hz, 1 H, H^{im}), 10.22 (d, J = 6.8 Hz, 1 H, H^{al}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.49 (C-1,2), 81.29 (C-3,6), 135.83 (=CH), 136.54 (C-4,5), 140.97 (=CH), 154.11 (C=N), 172.55 (NC=O), 189.56 (CH=O) ppm. HRMS (ESI+): calcd. for $C_{12}H_{10}N_2O_4$ [M + H]$^+$ 247.0719; found 247.0719 (–0.4 ppm error).

Study of Competitive Oxidative Addition of EPTN-NH$_2$ to Dimethyl Fumarate (4e) vs. Maleate (4f) in $CDCl_3$: Anhydrous K_2CO_3(2.30 g, 16.7 mmol), PhI(OAc)$_2$ (1.79 g, 5.6 mmol), **2**(1.00 g, 5.6 mmol), dimethyl maleate (2.33 g, 16.2 mmol), and dimethyl fumarate (2.34 g, 16.3 mmol) were mixed in $CDCl_3$ (30 mL). The mixture was stirred at room temperature and 10 NMR spectra of 10 0.5-mL aliquots were taken within 270 min. Reaction was complete in 4 h. Isolation of the product was carried out as described above. Yield of *trans*-aziridine **5e** was 42%.

Supporting Information (see also the footnote on the first page of this article): Copies of NMR spectra of all compounds and crystallographic data for compounds **5c** and **5f**.

CCDC-733493 (for **5c**) and -733494 (for **5f**) contain the supplementary crystallographic data for this paper. These data can be ob-

tained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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