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Hypervalent Iodine-Mediated Aziridination of Alkenes: Mechanistic Insights and Requirements for Catalysis

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Abstract: By detailed study of the possible side reactions in the previously reported aziridination of alkenes with *N*-aminoheterocycles mediated by hypervalent iodine reagents, the requirements to make this reaction catalytic in iodoarene have been determined. The reaction requires an oxidant that will oxidise iodoarenes but that does not oxidise alkenes, but it is possible that no such oxidant actually exists! A method in which the hypervalent iodine reagent can be recycled without the need for reisolation is possible. Further study into the mechanism of this reaction gives tentative evidence that the reaction proceeds through formation of an aminoiodane that reacts directly with the alkene, contrary to previous literature reports in which an acetoxyamine intermediate is suggested. The temperature effect of this reaction is remarkable.

Keywords: aziridines · hypervalent compounds · iodine · reaction mechanism · oxidation

Introduction

Aziridines are important intermediates in organic synthesis.[1] The strained three-membered ring allows such functions to be opened by a range of nucleophiles giving rise to, amongst others, 1,2-diamines,[2] 1,2-aminoalcohols[3] and 1,2-aminothiols.[4] There are three main synthetic routes to aziridines: dehydration of 1,2-aminoalcohols,[5] the reaction of a carbene equivalent with an imine (protected on nitrogen)[6] or the reaction of a nitrene equivalent with an alkene.[7] As yet, there remain few catalytic enantioselective syntheses of aziridines[8] especially those avoiding transition-metal catalysts. The use of (diacetoxyiodo)benzene to mediate the aziridination reaction between *N*-aminoheterocycles (especially *N*-aminophthalimide) and alkenes was reported by Che to be a wide-ranging method.[9] This offered an improvement on the previous work, mainly by Jones,[10] Rees[11] and Atkinson[12] in which the same transformation was reported to be mediated by lead tetraacetate. Che also reported that the same reaction could be mediated by a hypervalent iodine derivative of 4-iodoanisole generated in situ from the parent iodoarene and *meta*-chloroperoxybenzoic acid (*m*CPBA).[13] Yudin has also reported that the aziridination reaction between *N*-aminophthalimide and alkenes can be performed electrochemically.[14]

The direct conversion of alkenes with various *N*-aminoheterocycles by using non-toxic hypervalent iodine reagents makes Che's procedures appealing. Recent reports of the use of enantiopure hypervalent iodine(III) reagents to effect enantioselective transformations[15] along with the recent reports of the use of iodoarenes as catalysts in oxidation reactions[16] led us to believe that this reaction might provide a basis from which to develop a new enantioselective catalytic reaction by using enantiopure iodoarenes.[17]

To date, we have been unable to establish a catalytic variant of this reaction. In order to understand this failure, we have performed an extensive investigation into the proposed catalytic reaction and all possible side reactions that can occur when attempts are made to make the reaction catalytic. In addition, we have sought to understand further the mechanism of the reaction mediated by stoichiometric quantities of (diacetoxyiodo)benzene. The mechanism of this reaction appears to be highly complex. In this paper, we report on current findings and our new insights into this reaction.

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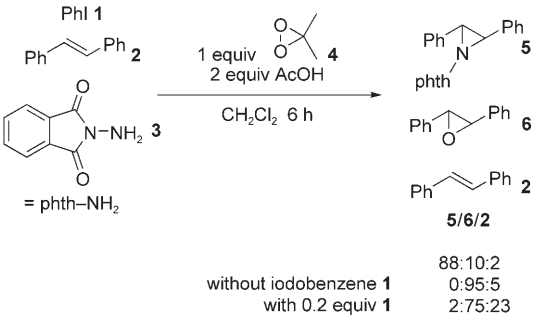
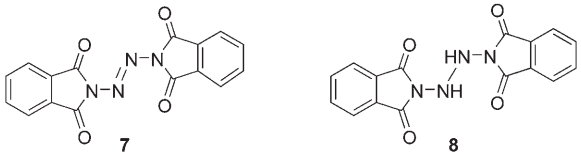
Results and Discussion

To begin development of a catalytic reaction, it is necessary to identify an oxidant that can oxidise an iodoarene selectively in the presence of the alkene and amine.[16a] A study of the literature suggested that dimethyldioxirane (**4**; DMDO) could fulfil that task.[18] An initial experiment in which one equivalent of DMDO was added to an equimolar mixture of iodobenzene (**1**), *trans*-stilbene (**2**) and *N*-aminophthalimide (**3**) in the presence of acetic acid in dichloromethane showed that the aziridine **5** is formed in good conversion with minimal formation of epoxide **6** (Scheme 1). In the absence of iodobenzene (**1**), epoxidation is the major pathway.

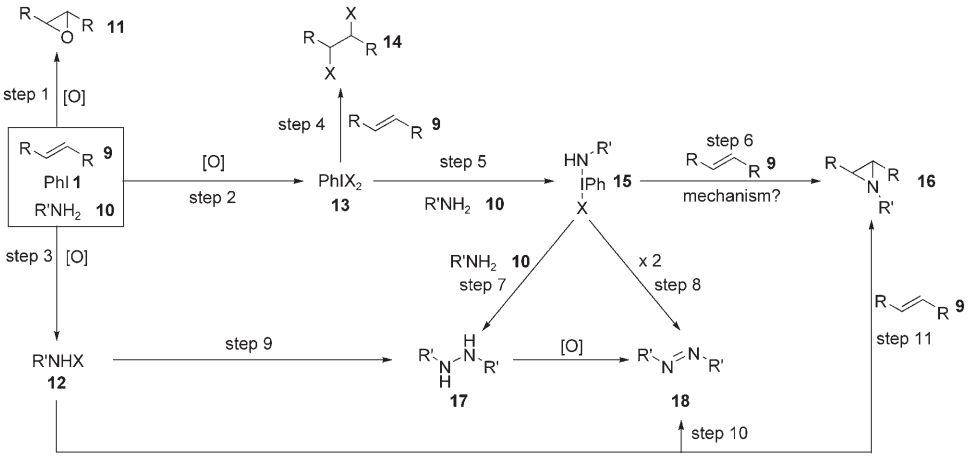


Scheme 1. Aziridination of stilbene by using DMDO with iodobenzene. Product ratios were determined by ^{1}H NMR spectroscopic analysis of the crude reaction products.

The use of substoichiometric iodobenzene did not result in formation of aziridine. Instead, large quantities of epoxide were detected (Scheme 1) along with unreacted *trans*-stilbene, tetrazene **7** and tetrazane **8**—known products of the oxidation of amine **3** in the absence of alkene.[19] Many attempts to obtain high yields of aziridine **5** by using substoichiometric iodobenzene by slow addition of *trans*-stilbene (**2**) and/or amine **3** were unsuccessful. After obtaining these results, we noticed Che's report of the use of in situ generated hypervalent iodine reagents for the same transformation also failed when substoichiometric iodoarene was used.[13] Repetition of our experiments by using *m*CPBA (as Che had used) in place of the DMDO used in our studies gave almost identical results. As Che had given no detailed explanation of the failure of his catalytic attempts, we decided to explore the possible side reactions in this system and determine their relative rates in order to determine what conditions, if any, could achieve catalysis in this reaction. In all reactions described here, both DMDO or *m*CPBA were used as oxidants without significant changes in the outcome. Additionally, all experiments were repeated in the presence or absence of acetic anhydride or acetic acid without significant changes.



The possible side reactions that could occur when a mixture of an alkene **9**, iodobenzene (**1**) and amine **10** are treated with an oxidant are shown in Scheme 2, along with possible routes to the desired aziridine **16**. When the mixture of compounds **9**, **1** and **10** are treated with an oxidant, oxidation of alkene **9** to epoxide **11** (step 1), **1** to the hypervalent iodine reagent **13** (step 2) or direct oxidation of amine **10** to **12** (step 3) are all possible. After formation of the hypervalent iodine reagent **13**, one must consider the reaction of this reagent directly with the alkene **9** to give difunctionalised alkane **14**[20] (step 4) and the ligand exchange reaction with amine **10** to give aminoiodane **15** (step 5). Aminoiodane **15** may then react with the alkene **9** giving aziridine **16** (step 6, the mechanism of this will be discussed in detail later), with further amine **10** giving tetrazane **17** (step 7) or with itself giving tetrazene **18** (step 8). In the presence of oxidant, tetrazane **17** is oxidised to tetrazene **18**. Additionally, aziridine **16**, tetrazane **17** and tetrazene **18** could conceivably be reached through oxidised amine **12** without need for the iodoarene (steps 11, 9, 10, respectively). We never observed 1,2-addition product **14**, suggesting that step 4 is not a significant reaction.[21] In the absence of iodobenzene **1**, aziridine **16** is never observed: if the oxidation is performed in the presence of alkene, only epoxide **11** is formed and if amine **10** is treated with oxidant first followed by addition of alkene **9** at intervals between 10 s and 10 h, either epoxide **11** or tetrazene **18** are formed. This suggests that once the amine **10** is oxidised to **12** directly by DMDO or

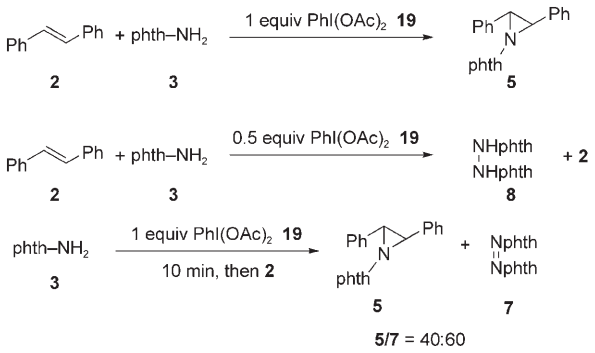


Scheme 2. Possible reactions on oxidation of the mixture of alkene, iodobenzene and amine.

*m*CPBA, conversion to aziridine **16** does not occur, highlighting the need for the iodoarene **1** or hypervalent iodine reagent **13** to be present and indicating that step 11 does not occur to any significant extent. Products of ring opening of epoxide **11** and aziridine **16** are never observed.

Attention was first turned to the oxidation of the three starting materials. As stated before, addition of oxidant to the mixture of alkene **9**, iodobenzene (**1**) and amine **10** gives a good conversion to aziridine **16**. In the absence of iodobenzene, only epoxide **11** was observed with no significant formation of the products of amine oxidation. As shown earlier, and in accord with the report by Che,[13] aziridination must proceed through the hypervalent iodine reagent **13**. These results show that iodobenzene **1** is oxidised faster that alkene **9** which in turn is oxidised faster than amine **10** so the reaction can proceed, as required, through hypervalent iodine reagents **13** and **15** (that is, along step 2, Scheme 2). In all cases, the reactions were left for 8 h, which is longer than any of the individual steps require to go to completion.

The direct reaction of the hypervalent iodine reagent **13** with alkene **9** to give difunctionalised alkane **14** (step 4) has already been excluded from the mechanism, so it can be assumed that **13** reacts only with amine **10** to give aminoiodane **15**. The relative rates of the reactions of aminoiodane

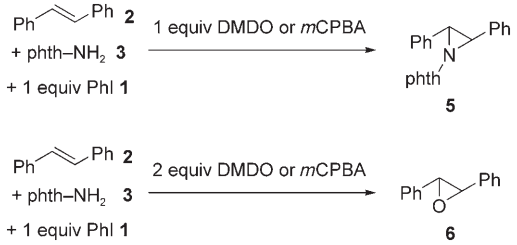


Scheme 3. Determining the fate of the aminoiodane **15**.

15 were determined by a series of experiments (Scheme 3). (Diacetoxyiodo)benzene (**19**) was used here as it is known that this will react only to give an aminoiodane such as **15**. Addition of stoichiometric oxidant **19** to a mixture of alkene **2** and amine **3** gives aziridine **5** as the major product. Use of substoichiometric oxidant **19** results only in tetrazane **8**. This suggests that, when aminoiodane **15** is generated in the presence of excess amine **3**, it reacts with the amine **3** (step 7, Scheme 2) faster than it does with the alkene **2** (step 6, Scheme 2). However, when stoichiometric oxidant is employed, the conversion of amine **10** to the aminoiodane **15** (step 5, Scheme 2) is faster than the formation of tetrazane **8** (step 7), leaving no amine around to react through this dimerisation pathway. If the amine is treated with stoichiometric oxidant **19** in the absence of alkene and the resulting mixture is treated with alkene after some time, aziridine **5** is formed along with tetrazene **7**. This shows that a pathway allowing direct dimerisation of the aminoiodane **15** does exist (step 8, Scheme 2), but this is slower than the formation of aziridine **5**. These results show that in any potential catalytic reaction, amine **10** must not be present in excess over the hypervalent iodine reagent **13** (and hence the stoichiometric oxidant and the iodoarene) and, therefore, must be added slowly to the reaction mixture.

When (diacetoxyiodo)benzene (**19**) is replaced with [bis(trifluoroacetoxy)iodo]benzene, the presence of hexamethyldisilylamine (HMDS) is necessary to prevent the trifluoroacetic acid generated in the reaction polymerising the alkene. The addition of HMDS or potassium carbonate has previously been reported as beneficial to the yield of the aziridination reaction.[9,22] When the more reactive [bis(trifluoroacetoxy)iodo]pentafluorobenzene[23] is used, very low conversions to aziridine are observed along with a large conversion to dimers **7** and **8**. This suggests that the more electron-poor arene accelerates the dimerisaton (step 7, Scheme 2) more than it accelerates the ligand exchange (step 5) so that the aminoiodane can no longer accumulate.[24] This is consistent with the steps that involve reducing the iodoarene being accelerated more than the ligand exchange steps.

The relative rates of the reactions of alkene **9** with the stoichiometric oxidant (step 1, Scheme 2), the hypervalent iodine reagent **13** (step 4) and the aminoiodane **15** (step 6) giving the epoxide **11**, addition product **14** or aziridine **16**, respectively, is an important factor in determining whether the aziridine can be formed. As previously discussed, the direct reaction between **13** and the alkene **9** (step 4) can be discounted. The relative rates of the remaining two can be determined by two experiments (Scheme 4). Oxidation of an

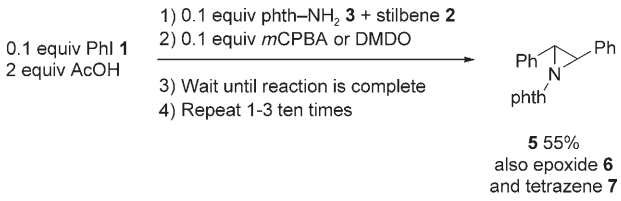


Scheme 4. Determining the fate of the alkene **2**.

equimolar mixture of stilbene **2**, amine **3** and iodobenzene **1** with one equivalent of DMDO or *m*CPBA gives a good conversion to aziridine **5**, whereas by using two equivalents of oxidant results in epoxide **6** as the major product. This suggests that alkene **2** reacts with aminoiodane **15** (to give aziridine) slower than it does with the stoichiometric oxidants used in this work. This means that in any potential catalytic reaction employing *m*CPBA or DMDO as the terminal oxidant, the oxidant must not be present in excess of the remaining iodobenzene at any time. This means that slow addition of the oxidant is necessary.

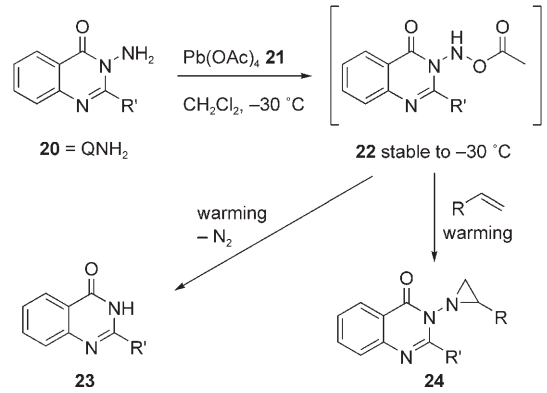
From these results, it would appear as if the both the amine and the oxidant must be added slowly to the reaction

mixture in order to obtain a reaction employing substoichiometric iodobenzene. The best-yielding procedure of this type is to use an in situ recycling modification of Che's procedure[13] in which an equilmolar solution of iodobenzene (**1**), *trans*-stilbene (**2**) and *N*-aminophthalimide (**3**) are oxidised by DMDO (the is reaction allowed to go to completion). Addition of further alkene **2** and amine **3** followed by further oxidant (repeated a total of ten times) gave aziridine **5** in 55% yield (Scheme 5). The low solubility of *N*-aminophthalimide (**3**) in all common organic solvents makes this procedure a very difficult one to follow. As it is unlikely to become practical, we abandoned development there. Another option for a simple catalytic procedure would be to add amine **3** slowly to a mixture of iodobenzene (**1**), alkene **2** and a stoichiometric oxidant which rapidly oxidises iodoarenes, but does not react with amines and generates hypervalent iodine reagents that do not react directly with alkenes. To date, we have found no such oxidant and we cannot see that one is likely to exist.



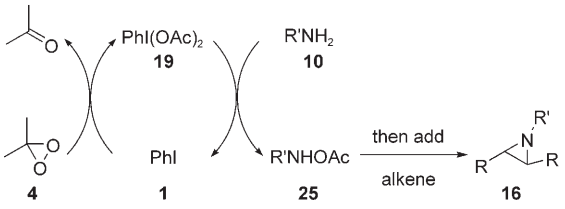
Scheme 5. In situ recycling of iodobenzene.

On closer inspection of the literature, another possible catalytic procedure came to light. The mechanism of the aziridination reaction between *N*-aminoheterocycles and alkenes mediated by lead tetraacetate was studied extensively by Atkinson.[25] He showed that treatment of *N*-aminoquinazolinones **20** with lead tetraacetate (**21**) gives rise to *N*-acetoxyamines **22** that are stable at −30 °C (Scheme 6). These then form aziridines **24** on treatment with alkenes or the parent heterocycle **23** (by dimerisation to and decomposition of the dimeric tetrazene[19d]) on warming. He also reports that *N*-acetoxyaminophthalimide (made in the same way) was stable up to −50 °C. The aziridination mediated by (diacetoxyiodo)benzene[13,25] and other related reactions[26] are believed to go through the same intermediate.



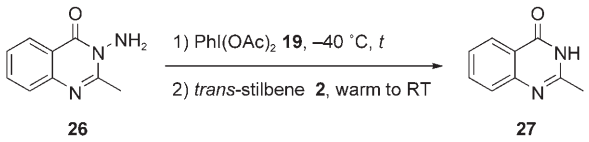
Scheme 6. Atkinson's mechanism for the aziridination mediated by Pb(OAc)$_4$.

If this is indeed the case, it should be possible to generate the *N*-acetoxyamino compound **25** by using catalytic iodobenzene (**1**) as shown in Scheme 7. Treatment of a mixture of *N*-aminoheterocycle **10** and iodobenzene (**1**) with DMDO in the presence of acetic acid or anhydride at low temperature should give (diacetoxyiodo)benzene (**19**) then aminoiodane **15** which can decompose to the stable acetoxyamine **25** regenerating catalyst **1**. Once oxidation of the amine **10** is complete, addition of the alkene and warming should give the aziridine **16**.



Scheme 7. Proposed catalytic generation of acetoxyamine **25**.

This was attempted at a range of temperatures, with *N*-aminoquinazolinones as well as *N*-aminophthalimides, with differing orders and rates of addition and with various sources of the acyloxy ligand. Only traces of aziridine **16** were ever observed—the only products being the tetrazene **7**, in the case of *N*-aminophthalimide, or the parent heterocycle **22** (believed to be a result of decomposition of the tetrazene[19]) when *N*-aminoquinazolinones are used. Some epoxide **6** can be detected if the alkene is added very quickly. It appeared that accumulation of the *N*-acetoxyamino compound **25** is not possible. To test this further, 2-amino-3-methylquinazolin-1-one (**26**) was oxidised at −30 °C with (diacetoxyiodo)benzene (**19**) and, at varying time intervals, the resulting solution was added to *trans*-stilbene (**2**) (Scheme 8). The only product detected was 3-methylquinazolin-1-one (**27**)—a result repeated at many temperatures between 0 and −60 °C. Use of *N*-aminophthalimide **2** gave only tetrazene **7**. Repeating Atkinson's experiment by using lead tetraacetate in place of (diacetoxyiodo)benzene gave a good yield (76%) of aziridine.



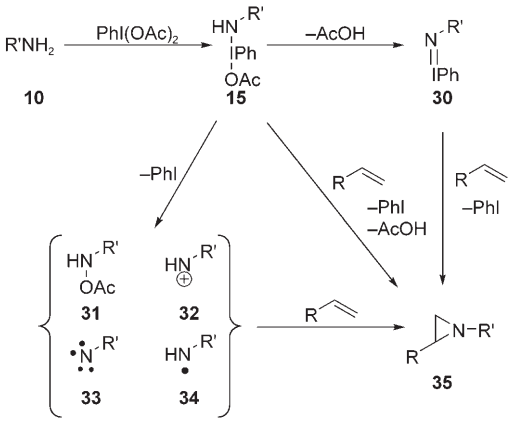
Scheme 8. Oxidation of *N*-aminoheterocycles before addition of alkene.

In light of these results, we propose that the aziridination mediated by (diacetoxyiodo)benzene (**19**) does not, in fact, proceed through the *N*-acetoxyamine at all, but that a differ-

ent intermediate was involved in reacting with the alkene. Atkinson had used competition experiments between electronically different alkenes to distinguish between intermediates in the lead tetraacetate mediated reaction.[25] Owing to the low solubility of some of the reagents used in this case, kinetic studies would prove difficult, so we decided to use a series of similar competition experiments to determine if the same intermediate was involved in the hypervalent iodine-mediated reaction.

In all cases, a mixture of the amine **10** and ten equivalents of a mixture of alkenes was oxidised by either lead tetraacetate (**21**) or (diacetoxyiodo)benzene (**19**) in dichloromethane solution. After allowing the reaction to proceed to completion, the ratio of the two aziridines were determined by integration of the ^{1}H NMR spectra. Ten equivalents of alkene were used because the excess means that the product ratio directly corresponds to the ratio of rate constants for the reaction with the two alkenes. There were concerns that the formation of "invertomers"[9,25] (diastereomers at nitrogen owing to slow lone pair inversion) might affect the accuracy of results determined by integration of the ^{1}H NMR spectrum. This problem is, however, avoided by use of monosubstituted alkenes or *cis*-disubstituted alkenes in which the thermodynamic invertomer ratio is greater than 95:5, or by the use of symmetrical *trans*-disubstituted alkenes; the invertomers of the aziridine correspond to enantiomers, not diastereomers (Table 1).

In all cases, the aziridinating agent reacts preferentially with the more electron-rich alkene. Under any set of conditions, the reaction using lead tetraacetate proved more selective than the corresponding reaction using (diacetoxyiodo)benzene. This cannot be a result of the lead(II) byproducts of this reaction because removal of these by low-temperature filtration (as performed by Atkinson[25]) results in no change in selectivity. These results suggest that the species that reacts with the alkene when the amine is oxidised by (diacetoxyiodo)benzene is not the same as that when lead tetraacetate is used and, hence, the acetoxyamine **22** is not on the reaction path. The addition of HMDS or potassium carbonate (bases sometimes added to these reactions to improve yield[22]) gave no significant change in the selectivity of the reactions, neither did the use of [bis(trifluoroacetoxy)iodo]benzene. This suggests that the role of the base is only to neutralise the acid generated in the reaction, and that the electronics of the reactive intermediate are not significantly affected by the acyloxy ligand on iodine. In order to pursue this mechanism further, a series of possible mechanisms was proposed (Scheme 9) and we set about investi-

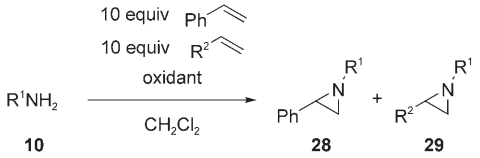


Scheme 9. Possible mechanisms for the aziridination reaction mediated by (diacetoxyiodo)benzene.

gating each in turn. Further experiments were performed by using the mixture of styrene and 3-nitrostyrene as this ensures that the difference in the alkenes is mostly electronic in nature.

The aziridination reaction can follow any of the following paths. After the ligand exchange reaction generates aminoiodane **15**, this could react directly with the alkene to give the aziridine **35**. Alternatively, acetic acid could be eliminated from the aminodane **15** generating iminoiodane **30** which could react with the alkene. Either of these intermediates could extrude iodobenzene to generate one of a series of intermediates: acetoxyamine **31**, nitrenium ion **32**, nitrene **33** or the nitrogen-centred radical **34**. These intermediates can then react with the alkene to make the aziridine **35**. From the experiments described earlier, the acetoxyamine **31** can already be eliminated so attention was turn to the other intermediates in turn.

Table 1. Rate comparison between alkenes under different aziridinating conditions.



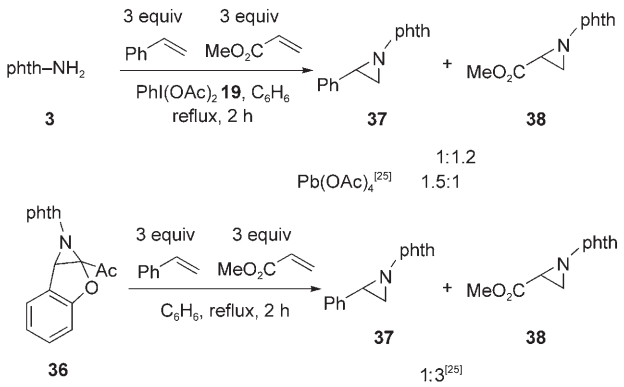
Entry	R^{1}[a]	R^{2}	T [°C]	Oxidant	**28**/**29**[b]
1	Q	MeO_2C	−25	$Pb(OAc)_4$	38:1
2	Q	MeO_2C	−25	$PhI(OAc)_2$	10:1
3	Q	3-$(NO_2)C_6H_4$	−25	$Pb(OAc)_4$	9.4:1
4	Q	3-$(NO_2)C_6H_4$	−25	$PhI(OAc)_2$	3.5:1
5	Q	4-$(Br)C_6H_4$	−25	$Pb(OAc)_4$	1.4:1
6	Q	4-$(Br)C_6H_4$	−25	$PhI(OAc)_2$	1.1:1
7	Q	3-$(NO_2)C_6H_4$	22	$Pb(OAc)_4$	4.2:1
8	Q	3-$(NO_2)C_6H_4$	22	$PhI(OAc)_2$	2.8:1
9	phth	3-$(NO_2)C_6H_4$	22	$Pb(OAc)_4$	3.8:1
10	phth	3-$(NO_2)C_6H_4$	22	$PhI(OAc)_2$	2.9:1

[a] Q = 3-methyl-1-oxoquinazolin-2-yl, phth = phthalimide. [b] Determined by integration of the crude 400 MHz ^{1}H NMR spectrum.

Radical intermediates such as **34** are known to be generated from hypervalent iodine reagents.[27] To investigate the possibility of a radical mechanism, the aziridination was performed by using *cis*- and *trans*-stilbene. Total conservation of stereochemistry was observed in each case, consistent with both C–N bonds being formed concertedly, hence the conclusion that the reaction is probably not a radical process. Further evidence against the presence of radical intermediates comes from competition experiments. When either *N*-aminophthalimide (**3**) or 2-amino-3-methylquinazolin-1-one (**26**) are oxidised by (diacetoxyiodo)benzene in the presence of excess 1,1-diphenylethene and *trans*-stilbene, preferential reaction is observed with *trans*-stilbene. The selective reaction with styrene is also seen when it is used in place of *trans*-stilbene. A radical intermediate would be expected to react preferentially with 1,1-diphenylethene[28] so it is unlikely that radical intermediate **34** is involved in the aziridination reaction.

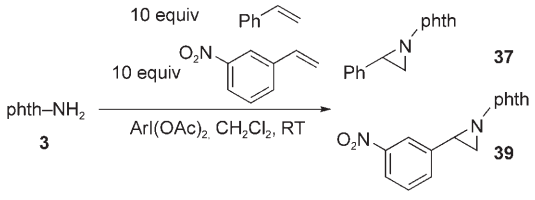
Attention was next turned to the iminoiodane **30**. Whilst *N*-sulfonyliminoiodanes and *N*-(trifluoroacetylimino)iodanes have been extensively reported[29] and have been shown to undergo aziridination of alkenes in the presence of transition-metal catalysts,[29a,30] no reports of iminoiodanes carrying electron-donating groups on the nitrogen atom exist. Preparation of iminoiodane **30** proved impossible, so attention was turned to the use of computational methods. Whilst *N*-(methanesulfonyl)iminoiodane can be located as an energy minimum at the B3LYP/6-31+G(d,p) level[31] by using the LANL2DZ(d,p) for iodine,[32] attempts to minimise *N*-phthalimidoiminoiodane **30** led to an activationless decomposition to iodobenzene and phthalimidonitrene **33**. Repeating the calculations by using the MP2 method and also when using a PCM solvation model for dichloromethane[33] gave the same results. Clearly, the iminoiodane **30** is not a minimum on the potential energy surface and would spontaneously decompose to the nitrene **33** so can be eliminated from the aziridination pathway.

Phthalimidonitrene (**33**) was, for many years, the intermediate thought to be involved in the aziridination of alkenes mediated by lead tetraacetate.[10] Atkinson used the thermolysis of aziridine **36** (derived from 2-acetylbenzofuran) in refluxing benzene to generate phthalimidonitrene (**33**) which was then reacted, irreversibly, with three equivalents of styrene and three equivalents of methyl acrylate.[25b] Under these conditions, the reaction proceeded preferentially with methyl acrylate (3:1 product ratio), whereas when the reaction was performed by using *N*-aminophthalimide **3** and lead tetraacetate in boiling benzene, preferential reaction was observed with styrene (1:1.5 product ratio). We performed an identical reaction employing (diacetoxyiodo)benzene (**19**) and detected preferential reaction with methyl acrylate but in a **37**/**38** 1:1.2 product ratio (Scheme 10). This was an interesting result, as in all other cases preferential reaction had been observed with the more electron-rich alkene. When performing the lead tetraacetate mediated reaction in benzene at room temperature, preferential reaction with styrene was observed. The product ratio at high temperature is different to that from the reaction believed to proceed via the nitrene.[19a,25b] In addition, the room temperature reaction shows the opposite selectivity to that observed in the nitrene reaction. From this we suggest, tentatively, that the aziridination reaction does not proceed through nitrene **33**.



Scheme 10. Investigating possible nitrene intermediates.

The remaining possible mechanisms are those proceeding via the nitrenium ion **32** or the direct reaction of the aminoiodane **15** with the alkene. Nitrenium ions have been proposed in other reactions of hypervalent iodine intermediates.[34] Given the hypernucleofugality[24] of the hypervalent iodine group in **15**, these intermediates would be expected to be electronically similar. Performing the aziridination reaction by using excess styrene and 3-nitrostyrene with electronically different (diacetoxyiodo)arenes leads to a changing ratio of aziridines (Scheme 11). The differences in the ratios are low, but suggest that the aryl iodide is present in the C–N bond-forming transition state. This is also further evidence against the involvement of the nitrene. Attempts were made to widen the range of the leaving group ability of the hypervalent iodine reagent in order to increase the effect on the product ratio. However, as mentioned earlier, the use of [bis(trifluoroacetoxy)iodo]pentafluorobenzene, which would lead to a much better nucleofuge, gives only tetrazene products and attempts to use the cyclic iodane 1-acetoxybenziodoxol-3-one, which should be a much poorer

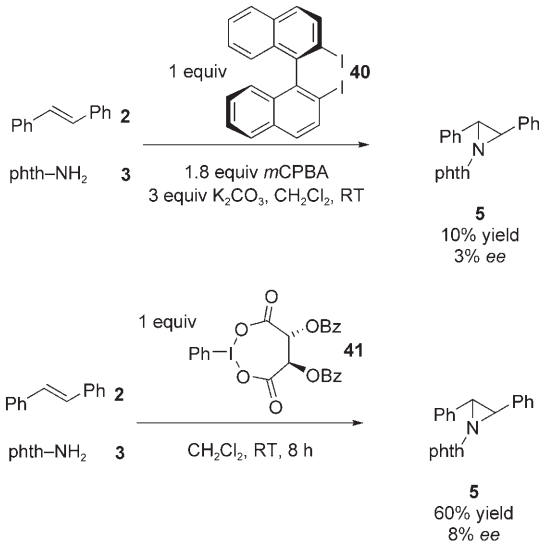


Ar:	Hammett σ	37/39
Ph–	0.00	2.9:1
3-(MeO)C_6H_4–	+0.12	3.3:1
3-(CF_3)C_6H_4–	+0.46	3.8:1

Scheme 11. Aziridination with electronically different (diacetoxyiodo)arenes.

leaving group entropically, led to recovery of starting materials.

Another test for the presence of the iodoarene in the C–N bond-forming step would be enantiocontrol when the reaction is performed with an enantiopure hypervalent iodine reagent. Owing to the problems encountered in the oxidation of some chiral iodoarenes,[17] attention was turned to the in situ generation of these reagents in a reaction reported by Che.[13] Repetition of some of the styrene/3-nitrostyrene competition experiments by using Che's procedure showed that the selectivity of the reaction was the same as that obtained by using (diacetoxyiodo)benzene. This suggests that the reaction proceeds through essentially the same mechanism for which, as shown earlier, the acyloxy ligand on iodine does not affect the selectivity. Use of chiral iodoarene **40**[35] under Che's conditions gave a low yield of aziridine **5** in 3% *ee* (*ee* = enantiomeric excess, Scheme 12).



Scheme 12. Use of a chiral iodoarene **40** under Che's conditions or stoichiometric chiral hypervalent iodine reagent **41**.

This small enantioinduction is further tentative evidence for the presence of the iodoarene in the transition state for C–N bond formation. The use of enantiopure iodane **41**,[36] in which the chirality is present in the acyloxy ligand and not in the arene, also gave some enantioinduction, suggesting that the acyloxy function is also present in the transition state for bond formation even though the electronics of this group do not appear to affect the selectivity in the competition experiments.

The evidence presented here suggests that the mechanism of the hypervalent iodine-mediated azirdination of alkenes at room temperature proceeds by means of a ligand exchange reaction, generating an aminoiodane **15** which reacts directly with the alkene such that the iodoarene is present in the transition state for C–N bond formation. The aminoiodane **15** can be calculated as a minimum on the PES at the HF/LANL2DZ level (Figure 1), consistent with it being an intermediate in the reaction. The other intermediates **31**–**34** proposed in Scheme 9 are also minima at the B3LYP/6-31+G(d,p) level. No transition states for the interconversion of these intermediates or the conversion of these intermediates to any aziridine (except in the case of nitrene **33**) have been located, so attempts to study the preferred pathway by computational means have so for been unsuccessful.

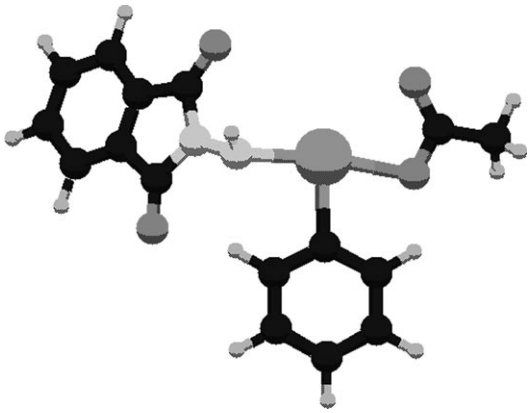


Figure 1. Structure of aminoiodane **15** at the HF/LANL2DZ level.

However, there are a number of questions remaining regarding the temperature dependence. Firstly, why does the sense of selectivity between styrene and methyl acrylate in benzene change when the reaction is heated to reflux? Secondly, the selectivity in the reaction of aminoquinazoline **20** with styrene and 3-nitrostyrene mediated by lead tetraacetate shows an expected decrease on increasing the temperature from −25 to 22 °C (Table 1, entries 3,7), but the same reaction mediated by (diacetoxyiodo)benzene showed a very much smaller decrease (Table 1, entries 4,8). To attempt to understand both these factors, the selectivity in the reactions of aminoquinazoline **20** with excess styrene and 3-nitrostyrene mediated by lead tetraacetate and by (diacetoxyiodo)benzene in dichloromethane was investigated at a range of temperatures (Figure 2).

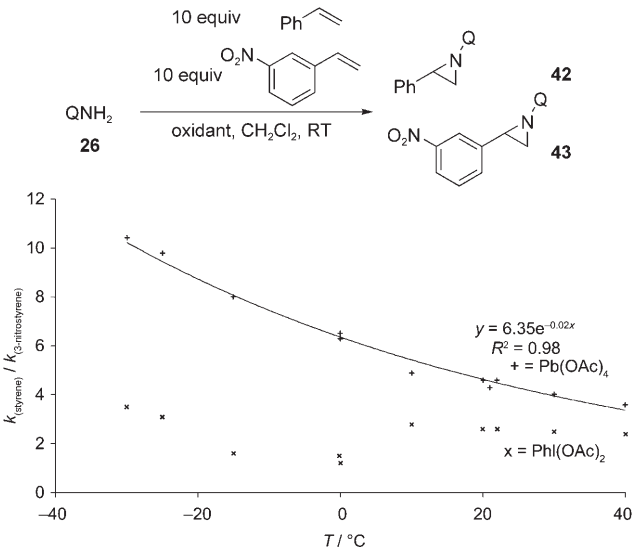


Figure 2. Relative rate of reaction of aminoquinazoline **26** with styrene and 3-nitrostyrene at a range of temperatures.

The relative rate of reaction with the different amines showed the expected exponential temperature dependence when the reaction is mediated by lead tetraacetate. The reaction using (diacetoxyiodo)benzene exhibits an apparent discontinuity between 0 and 10 °C. This suggests that a change in the mechanism may occur at this temperature, but we have been unable to investigate this further. When the experiment is repeated by using *N*-aminophthalimide, the temperature profile is even more remarkable (Figure 3).

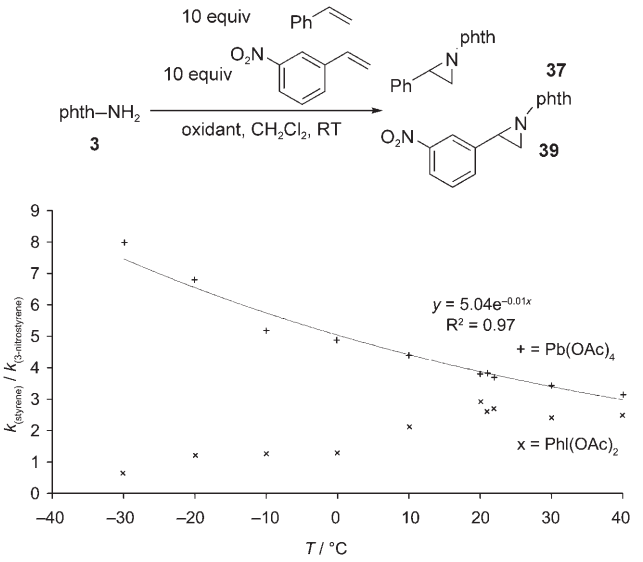


Figure 3. Relative rate of reaction of *N*-aminophthalimide (**3**) with styrene and 3-nitrostyrene at a range of temperatures.

In this case, the selectivity in the reaction decreases as the temperature is decreased below 20 °C. This may, in part, be due to the insolubility of *N*-aminophthalimide (and some of its derivatives) below −10 °C. Also in this case, the sense of selectivity is seemingly reversed at −30 °C. We cannot offer any definite explanations for this effect.

Conclusion

Detailed studies of the side reactions that occurred in our attempts have shown that the requirement for this catalytic reaction is an oxidant that can oxidise iodoarenes to the iodine(III) reagent but which do not oxidise alkenes or give rise to hypervalent iodine reagents that react with alkenes. We know of no such reagent. Without this reagent, the closest we can get to a catalytic reaction is by performing an in situ recycling of the iodane. Further study into the (diacetoxyiodo)benzene-mediated aziridination reaction suggests that the mechanism of this reaction at room temperature involves a ligand exchange to generate an aminoiodane which reacts directly with the alkene. This suggests that a stereoselective variant of this reaction using enantiopure iodanes might well be possible. This conclusion is rather tentative as the evidence ruling out iminium-ion intermediates is not decisive. The hypervalent iodine-mediated reaction shows a remarkable temperature dependence that is not observed in the lead tetraacetate mediated reaction. To date we can offer no convincing explanation of these temperature effects. We feel that this work has implications for other reactions that involve the *N*-aminophthalimide/(diacetoxyiodo)-benzene reagent combination.

Experimental Section

General methods: Aziridination reactions were conducted by using commercial laboratory grade solvents without purification. (Diacetoxyiodo)arenes were prepared according to the procedure of McKillop,[37] [bis(trifluoroacetoxy)iodo]benzene was purchased from commercial sources, [bis(trifluoroacetoxy)iodo]pentafluorobenzene was prepared by the procedure of Schmeisser,[38] 1-acetoxybenziodoxol-3-one was prepared by the procedure of Tetlow,[39] 2,2′-diiodo-1,1′-binaphthyl (**40**) was prepared by the method of Murdoch[35] and tartrate-derived chiral iodane **41** was prepared by the method of Imamoto.[36] Lead tetraacetate was recrystallised from acetic acid before use. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 or Bruker Avance 500 BB against an internal deuterium lock. Melting points are uncorrected.

General procedure for aziridination reactions: A solution of oxidant (0.12 mmol) in dichloromethane (1 mL) was added to a mixture of alkene (0.10 mmol) and amine (0.11 mmol) in dichloromethane at room temperature. After stirring for 6 h, the reaction was quenched by addition of saturated aq sodium carbonate (2 mL) and extracted with ethyl acetate (3×2 mL). The combined organic extracts were washed with saturated aq sodium chloride (5 mL), dried over sodium sulfate and concentrated under reduced pressure. If necessary, the products were purified by flash column chromatography (silica gel, hexane/ethyl acetate).

General procedure for competition experiments: A solution of oxidant (0.12 mmol) in dichloromethane (1 mL) was adjusted to the reaction temperature and added to a mixture of alkenes (1 mmol of each), amine (0.1 mmol) and base (0.3 mmol if required) in dichloromethane (2 mL) at the specified reaction temperature. The reaction was stirred until all amine had been consumed (TLC) and was then quenched by addition of premixed saturated aq sodium carbonate (2 mL), saturated aq sodium thoisulfate (2 mL) and saturated aq potassium iodide (0.5 mL). This mixture was then extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with saturated aq sodium chloride (5 mL), dried over sodium sulfate and concentrated under reduced pressure. The ratio of aziridines was determined by ^{1}H NMR spectroscopic analysis of the crude products by integrating the signals for the protons on the aziridine ring between $\delta = 4.00$ and 2.70 ppm.

Representative procedure for reactions involving in situ generation of hypervalent iodine reagents and attempted catalytic reactions: *m*CPBA (0.1 mmol) or dimethyldioxirane (0.1 mmol, 0.1 M solution in acetone) were added to a solution of iodoarene (0.1 mmol), amine (0.1 mmol) and alkene (0.1 mmol) in dichloromethane (2 mL). After the oxidant had been consumed (typically 3 h for DMDO, 12 h for *m*CPBA), the reaction was quenched by addition of premixed saturated aq sodium carbonate (2 mL), saturated aq sodium thoisulfate (2 mL) and saturated aq potassium iodide (0.5 mL) and was then extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with saturated aq sodium chloride (5 mL), dried over sodium sulfate and concentrated under reduced pressure. The product ratios were determined by ^{1}H NMR spectroscopic analysis on the crude products.

2-[(2*RS*,3*RS*)-2,3-Diphenylaziridin-1-yl]isoindoline-1,3-dione (5): Yield: 85 % from *trans*-stilbene (**2**), *N*-aminophthalimide (**3**) and (diacetoxyiodo)benzene (**19**). Spectroscopic data consistent with that previously reported.[40] Enantiomeric excess determinations were carried out by using a Chirapak AD column eluting with hexane/2-propanol 90:10 at a flow rate of 0.5 mL min^{-1} at room temperature.

2-[(2*RS*,3*SR*)-2,3-Diphenylaziridin-1-yl]isoindoline-1,3-dione: Yield: 79% from *cis*-stilbene, *N*-aminophthalimide (**3**) and (diacetoxyiodo)benzene (**19**). Spectroscopic data were consistent with that previously reported.[40]

2-(2,2-Diphenylaziridin-1-yl)isoindoline-1,3-dione: Yield: 75% from 1,1-diphenylethene, *N*-aminophthalimide (**3**) and (diacetoxyiodo)benzene (**19**). Spectroscopic were data consistent with that previously reported.[41]

2-(2-Phenylaziridin-1-yl)isoindoline-1,3-dione (37): Yield: 78% from styrene, *N*-aminophthalimide (**3**) and (diacetoxyiodo)benzene (**19**). Spectroscopic data were consistent with that previously reported.[11]

2-Methyl-3-(2-phenylaziridin-1-yl)quinazolin-4(3*H*)one (42): Yield: 84% from styrene, 2-amino-3-methylquinazolin-1-one (**26**) and (diacetoxyiodo)benzene (**19**). Spectroscopic data were consistent with that previously reported.[11]

3-[2-(4-Bromophenyl)aziridin-1-yl]-2-methylquinazolin-4(3*H*)one (29) (R^1=Q, R^2=4-BrC_6H_4): Yield: 65% (waxy solid) from 4-bromostyrene, 2-amino-3-methylquinazolin-1-one (**26**) and (diacetoxyiodo)benzene (**19**). IR (film): $\tilde{\nu}$=2924, 1675, 1598, 1472, 1328, 908, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.17 (1H, dd, J=8.0 1.3 Hz), 7.64 (1H, td, J=7.0, 1.3 Hz), 7.60 (1H, d, J=7.0 Hz), 7.54 (2H, d, J=8.0 Hz), 7.46 (1H, td, J=6.6, 1.8 Hz), 7.39 (2H, d, J=8.0 Hz), 3.58 (1H, dd, J=8.0, 5.6 Hz), 3.00 (1H, dd, J=8.0, 2.4 Hz), 2.82 (1H, dd, J=5.6, 2.3 Hz), 2.60 ppm (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ=160.0, 153.8, 146.0, 135.5, 134.0, 131.8, 131.6, 128.3, 126.5, 126.3, 122.2, 121.4, 47.2, 43.8, 22.0 ppm; LRMS (ESI−H^+): m/z (%): 359.0 (18) 358.0 (97), 357.0 (18), 356.0 (100) $[M+H]^+$; HRMS: calcd for $C_{17}H_{15}{}^{79}BrN_3O^+$: 356.0393; found: 356.0395 $[M+H]^+$.

Methyl 1-(1,3-dioxoisoindolin-2-yl)aziridine-2-carboxylate (38): Yield: 65% from methyl acrylate, *N*-aminophthalimide (**3**) and (diacetoxyiodo)-benzene (**19**). Spectroscopic data were consistent with those previously reported.[11]

Methyl 1-(2-methyl-4-oxoquinazolin-3(4*H*)yl)aziridine-2-carboxylate (29) (R^1=Q, R^2=CO_2Me): Yield: 58% from methyl acrylate, 2-amino-3-methylquinazolin-1-one (**26**) and (diacetoxyiodo)benzene (**19**). Spectroscopic data were consistent with those previously reported.[11]

2-[2-(3-Nitrophenyl)aziridin-1-yl]isoindoline-1,3-dione (29) (R^1=Phthal, R^2=3-(NO_2)C_6H_4): Yield: 71% from 3-nitrostyrene, *N*-aminophthalimide (**3**) and (diacetoxyiodo)benzene (**19**). IR (nujol mull): $\tilde{\nu}$=1783, 1720, 1529, 1346, 1159, 881, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=8.24 (1H, t, J=1.8 Hz), 8.13 (1H, dt, J=7.9, 1.3 Hz), 7.77–7.33 (3H, m), 7.68–7.64 (2H, m), 7.50 (1H, t, J=8.0 Hz), 3.61 (1H, dd, J=8.0, 6.5 Hz), 2.93 (1H, dd, J=8.0, 2.5 Hz), 2.74 (1H, dd, J=6.5, 2.5 Hz) 2.71 ppm (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ=164.9, 138.8, 135.1, 134.3, 133.4, 130.2, 129.6, 124.5, 123.3 ppm; HRMS: calcd for $C_{16}H_{12}N_3O_4^+$: 310.0822; found: 310.0825 $[M+H]^+$. Compound previously reported[42] but no NMR data were found.

2-Methyl-3-[2-(3-nitrophenyl)aziridin-1-yl]quinazolin-4(3*H*)one (29) (R^1=Q, R^2=3-$NO_2C_6H_4$): Yield: 43% from 3-nitrostyrene, 2-amino-3-methylquinazolin-1-one (**26**), and (diacetoxyiodo)benzene (**19**) as an amorphous solid. IR (nujol mull): $\tilde{\nu}$=1676, 1595, 1531, 1344, 884, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=8.24 (1H, t, J=1.9 Hz), 8.14 (2H, td, J=6.9, 1.8 Hz), 7.81 (1H, d, J=7.6 Hz), 7.66 (1H, td, J=6.9, 1.3 Hz), 7.55 (1H, d, J=8.1 Hz), 7.54 (1H, t, J=8.0 Hz), 7.39 (1H, t, J=7.1 Hz), 3.89 (1H, dd, J=8.0, 5.5 Hz), 3.01 (1H, dd, J=8.0, 2.0 Hz), 2.84 (1H, dd, J=5.5, 2.1 Hz) 2.71 ppm (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ=158.7, 152.6, 147.6, 137.8, 133.2, 132.1, 128.7, 125.6, 125.3, 122.1, 120.7, 120.3, 45.2, 42.8, 21.5 ppm; HRMS: calcd for $C_{17}H_{15}N_4O_3^+$: 323.1139; found: 323.1141 $[M+H]^+$.

Acknowledgements

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