Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: http://orca.cf.ac.uk/96412/

This is the author’s version of a work that was submitted to / accepted for publication.

Citation for final published version:


Please note:
Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher’s version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.
Iodoaminations of Alkenes

Pushpak Mizar, a Thomas Wirth*a

a School of Chemistry, Cardiff University, Park Place, Main Building, Cardiff CF10 3AT, UK
Fax: (+44) 29-2087-6968, E-mail: wirth@cf.ac.uk

Received: The date will be inserted once the manuscript is accepted.

Abstract: The activation of alkenes and their subsequent functionalization is a frequently used methodology in synthetic chemistry. This review highlights recent iodine-mediated aminations and elaborates on the various strategies to bring about regio- or stereoselective transformations.

1 Introduction

The utility and application of functionalized small molecules as drugs have encouraged many chemists in search of new methods to introduce functionalities.1 The functionalization of an unsaturated bond promoted by an electrophile is a frequently used synthetic method in organic chemistry.2 A typical example is the cyclofunctionalization, where an external electrophile activates an alkene containing an internal nucleophile leading to a cyclized product. Thus, adding an electrophile to suitable unsaturated amines can promote a regio- and stereoselective synthesis of heterocyclic motifs, which can be further functionalized with other nucleophiles.3 The iodine-mediated activation of double bonds is a very reliable transformation in synthetic organic chemistry (Scheme 1).5

![Scheme 1](image)

Scheme 1 Electrophilic iodine addition to alkenes.

2. Strategies and Mechanisms

Iodine as an electrophile for the activation of double bonds and subsequent intra- or intermolecular attack of a nucleophile has been employed as a highly successful strategy for the synthesis of various organic compounds. There are many source of iodine electrophiles for the iodoxygenation, and usual reaction condition involves the use of a basic solution of elemental iodine or KI. Iodonium acetate, N-iodosuccinimide (NIS) or bis-pyridine iodonium tetrafluoroborate can also be used as sources of I+. Hypervalent iodine compounds such as (diacetoxyiodo)benzene can also be used as efficient electrophiles.5

The regiochemistry of an electrophilic additions reaction is influenced by electronic as well as by steric factors.6 The conformation and reaction conditions can also direct the regioselectivity either towards 5-exo or 6-endo cyclizations, however, ring closures, under kinetic control usually proceed through the exo-modes (Scheme 2).

![Scheme 2](image)

Scheme 2 Regioselectivity in iodoaminations.

The kinetic or thermodynamic conditions utilized in the reaction are very important for the determination of the regiochemistry.7 Iodine addition to unsaturated amines usually promotes a regio- and stereoselective synthesis of heterocyclic motif; these intermediates can serve as valuable tools in chirality transfer reactions. Iodo-functionalization of double bonds is a stereospecific process resulting in an 1,2-anti product. The reaction typically proceeds via cyclic iodonium ions formation, followed by backside attack of the nucleophile yielding selectively an anti stereoisomeric product. Iodonium ions were observed by Olah et al., who reported that iodonium are cyclic on the 1H NMR time scale at ~60 and ~80 °C in liquid SO2.8

Another factor playing an important role in enantioselective iodoaminations is a possible olefin-to-olefin transfer that may racemize enantiomerically enriched iodonium ions and hence must be suppressed for enantioselective reactions provided that it is faster than the nucleophilic capture (Scheme 3).9

![Scheme 3](image)

Scheme 3 Olefin-to-olefin transfer of iodonium ions.

3. N-Functionalization of Alkenes
Iodoamination of unsaturated imidates is an important process for the synthesis of aminoalcohols. Such iodoaminations were performed by adding either I₂ in THF, or pyridine, as well as NIS in chloroform i.e. a kinetic condition. \(^{10}\) Cyclization of allylic substrates such as 1 with terminal double bonds showed complete regioselectivity to yield 4,5-dihydro-1,3-oxazoles 2 as 5-endo products while homoallylic derivatives 3 afforded 6-eno derivatives of type 4 (Scheme 4). The nature of the substitution has a major influence on the stereoselectivity, typically higher selectivities are obtained with larger substituents.

![Scheme 4 Iodoamination of allylic and homoallylic imidates.](image)

Several other factors influence the regioselectivity of acyclic allylic imidates. The regioselectivity depends on the reaction conditions employed (I₂/pyridine in THF; NIS in CHCl₃; I₂ in CHCl₃). The regiochemistry of the product is also influenced by the double bond configuration. The 6-membered rings product formation can be easily established by IR spectroscopy, the absorption band at 1670 cm⁻¹, which is similar to C=N stretch in a 6-membered ring of 2-trichloromethyl-4,5-dihydro-1,3-oxazines. Absorption at 1650 cm⁻¹ corresponds to 2-trichloromethyl-4,5-dihydro-1,3-oxazoles. \(^{11}\)

\((-\text{-})\)-Methyl ravidosamine 7, a component of the antibiotic ravidomycin 8, had been synthesized using the iodoamination as the key synthetic step. N-Methyliodoniumimidodithioate derivative 5, obtained from tri-O-acetyl-D-glucal, was cyclized to the altropyranose derivative 6 as shown in Scheme 5. \(^{12}\)

A direct iodoamination also constituted the important step in the total synthesis of an alkaloid extracted from Stemonaceae i.e. (+)-croomine 11. The double cyclization of 9 in a single step involves the formation of the iodoaminated product intermediate 10, which subsequently undergoes nucleophilic anchimeric assistance by the vicinal tertiary amine. A net retention of configuration at position C-14 and the formation of the vicinal pyrrolidino butyrolactone occurs by intramolecular capture of the intermediate aziridinium salt by the neighboring ester (Scheme 6). \(^{13}\) A similar methodology of ring-closing iodoamination has been employed in the synthesis of other natural products such as (−)-codonopsine, tropane alkaloids such as (−)-pseudococaine and various polyhydroxylated pyrrolidines. \(^{14}\)

![Scheme 5 Synthesis of ravidomycin 8 involving an iodoamination as the key step.](image)

A similar approach has been employed in the synthesis of a β-lactam ring by the iodoamination of 4-(3′-butenyl)azetidin-2-one initiated by iodine as the electrophilic reagent as shown in Scheme 7. An attack of the nitrogen atom on the iodonium ion of unsaturated amides can be achieved by replacing an amide proton with an electron-withdrawing group. It is observed that a lower pKa of the carboxamido group leads to the imide anion. Hence, the nitrogen atom becomes the most nucleophilic centre of the amide moiety.

![Scheme 6 Synthesis of (+)-croomine 11.](image)
Five and six-membered iodolactams were prepared by cyclization of $N,O$-bistrimethylsilyl derivatives of unsaturated amides with help of I$_2$ in THF. This procedure was employed for the conversion of several unsaturated amides to their corresponding iodolactams. The stereochemistry of the lactones matched those of the related lactones obtained using Bartlett’s thermodynamic reaction conditions.

An interesting methodology for the formation of $\gamma$-lactams involved iodine mediated cyclization of 3-substituted-4,5-unsaturated thioamidates. It proceeds with high regio- and stereoselectivity and the configuration of the major diastereomer was determined to be 4,5-cis. However, for 2-alkyl-4,5 unsaturated thioamidates, iodolactamization occurs with a high 1,3-trans selectivity due to the preference for quasi-axial orientation in the intermediate rather than the 1,3-di-quasi-equatorial orientation dictated by the strain between the $\alpha$-substituents and the methylthio group.

Bonjoch and co-workers carried out the iodoaminocyclization of homoallylic secondary amines with NIS to obtain 6-endo products as illustrated in Scheme 10. This work provided insight into the kinetic vs. thermodynamic control of iodoaminocyclizations using NMR analysis. Formation of 6-endo piperidine derivatives was thermodynamically favoured while the 5-exo-trig route leading to the formation of pyrrolidines was kinetically favoured.

In the iodoamidocyclization of unsaturated substrates having ambident nucleophiles such as carbamates, ureas or amides, $O$-cyclized products are usually obtained in preference over $N$-cyclized products. This was explained with the help of the HASB theory. Oxygen is more electronegative than nitrogen atoms; hence they prefer to attack the iodine-olefin $\pi$-complex that is characterized as a hard electrophile. To obtain $N$-cyclized products the pKa values need to be lowered with the help of $N$-substitution, e.g. $N$-tosylcarbamates ($X = O$) and $N$-tosylamides ($X = CH_2$) which have lower pKa values and provide $N$-cyclized products. Similar products are obtained with $N,O$-bis(trimethylsilyl) derivatives of 4-alkenamides ($X = CH_2, R = H$). However, these silyl derivatives lead to limited reactivity of the substrates.

Taguchi and co-workers carried out the iodoaminocyclization of unsaturated carbamates, ureas and carboxamides through regiocontrol of these ambident nucleophiles with the help metallic reagents. The $O$-cyclized product as a single isomer was obtained during iodoamidocyclization of $N$-ethoxycarbonyl-$N'$-allylurea under normal conditions (iodine, NaHCO$_3$). However, the $N$-cyclized product was obtained in a good yield with almost complete regioselectivity when the reaction was performed using a lithium reagent [n-BuLi or LiAl(Ot-Bu)$_2$]. The selectivity for $N$-cyclization was drastically influenced by the metallic reagents employed for example the use Al(Ot-Bu)$_3$ and Ti(Ot-Bu)$_4$.
The same group carried out iodoaziridination reactions using iodoaminocyclizations. Initial reaction of \(N\)-allylic tosylamide with \(I_2\), NIS or NBS afforded either an intermediate \(I_2\) addition product of olefin or no reaction was observed because of the low nucleophilicity of tosylamide. The use of \(t\)-BuOK was found to be the most effective for the activation of the tosylamide, superior to metallic reagents.\(^{20}\)

4. Enantioselective Iodoaminations

There are various strategies to perform stereoselective iodocyclizations. A chiral Lewis base can coordinate with an iodonium ion intermediate acting as a Lewis acid, which should be stable enough and not dissociate before the nucleophilic capture of the iodonium ion (Type 1). The interaction between the Lewis acidic iodonium ion intermediate and the catalyst could also be coulombic rather than dative, as the stronger interaction means that there is a continuous association of ion pairs (Type 2).\(^{23}\)

A coordination site on the substrate can also be used for the association of the chiral catalyst avoiding a direct interaction with the intermediate iodonium ion. This is possible by employing hydrogen-bonding interactions between the catalyst and the substrate to maintain a close distance with the iodonium ion intermediate (Type 3). Finally, to utilize the basic site of the substrate for interaction with a chiral Lewis acid to create a chiral environment for an activated capture of the iodononium ion by a nucleophile (Type 4).

Jacobsen and co-workers developed chiral Schiff-base derived catalysts such as 18 for the iodoacylation of alkenyl trichloroacetimides in the stereoselective vicinal iodoamination of the olefins to yield the corresponding products 19.\(^{21}\)

Kim and co-workers carried out iodoaminocyclization with trichloroacetimides as the nucleophile in the synthesis of \((+)-polyoxamic acid. The cyclization involved regioselective and stereoselective cyclization using a chiral starting material.\(^{22}\)

Chiral metal catalysts have also been utilised in stereoselective iodoaminations. Feng and co-workers employed scandium-based catalyst 20 for intermolecular iodoamination of chalcones and \(\alpha,\beta\)-unsaturated-\(\gamma\)-ketoesters resulting in the formation of \(\beta\)-sulfonamido-\(\alpha\)-iodo carbonyl products in high yields and with good enantioselectivity. Only low amounts of catalyst were necessary as shown in Scheme 14. The proposed mechanism for activation of iodine involves the reaction of \(N\)-chlorosuccinimide (NCS) with iodine for a slow release of ICI, which then reacts further by the formation of a Lewis-acidic catalyst complex. In another hypothesis, NCS oxidizes scandium to a higher oxidation state with increased Lewis acidity for an activation of the iodine.\(^{23}\)
Wirth et al. reported a catalytic method for the enantioselective iodoamination of alkenes using a novel chiral organocatalyst 22. A control of the regio- and stereoselectivity was possible. The addition of catalytic amounts of KI or KBr as additive leads to the formation of a more reactive iodinating species, which strongly influences the regioselectivity. The enantioselectivity was directed through a thiourea-based catalyst, which was able to interact via halogen bonding between the Lewis-basic sulfur centre and the electrophilic halogen-activated alkene leading to enantioselective heterodifunctionalized products 23 and 24 (Scheme 16). Product 24 is unstable so that the ee could not be determined.

Scheme 16 Regio- and stereoselective iodoamination with organocatalyst 22.

5. Conclusions and Outlook
This short review surveys the efficacy and versatility of iodine to activate unsaturated systems bringing about various chemical reactions. The review discusses the strategies employed for iodoamination cyclizations and further highlights the mechanisms involved. The review also sheds light on the application of additives or catalysts for regio- or stereoselective reactions.

The chemistry of iodoamination is still in its infancy as compared to the wide spread field of boron or metal-based amination reactions. However, there is a need to come up with efficient methods to curtail the reactivity of iodine mediated reactions. Future work should focus on the development of efficient catalytic systems for stereoselective iodoamination, thereby curtailing side reactions and stability issues observed with iodoamination.

Acknowledgment
This project was supported by an EU Marie Curie fellowship to P.M. (DIALMEC, No. 298642).

References
(1) Bougault, M. J. R. *Acad. Sci.* 1904, 139, 864.


Pushpak Mizar

Pushpak Mizar was a Marie Curie Fellow at Cardiff University. He completed his formal education at St. Edmunds College, NEHU and JNCASR, Bangalore. He then joined the Wirth group as a Marie Curie Fellow in 2012, funded by the European Commission. He was awarded Junior Research Fellowship by CSIR, India; Postgraduate Merit award and was a State Rank holder. He represented Cardiff University at the prestigious Lindau Noble Laureate Meeting in 2013. His research interest lies in designing synthetic methodology for asymmetric synthesis, green chemistry, chemical epigenetics and drug discovery.

Thomas Wirth

Thomas Wirth is professor of organic chemistry at Cardiff University. He received his PhD after studying chemistry at Bonn and the Technical University of Berlin. After a postdoctoral stay at Kyoto University as a JSPS fellow, he worked independently at the University of Basel before taking up his current position at Cardiff University in 2000. He was invited as a visiting professor to a number of places: Toronto (1999), Tokyo (2000), Osaka (2004, 2008), Kyoto (2012). He was awarded the Werner-Prize from the New Swiss Chemical Society (2000), the Furusato award from JSPS London (2013), the Wolfson Research Merit Award from the Royal Society (2016) and the Bader-Award from the Royal Society of Chemistry (2016). In 2016 he was elected as a fellow of The Learned Society of Wales. His main interests of research concern stereoselective electrophilic reactions, oxidative transformations with hypervalent iodine reagents and flow chemistry performed in microreactors.
Iodoaminations of Alkenes

Graphical Abstract

\[
\begin{align*}
\text{INTERMOLECULAR IODOAMINATION} & \quad \text{INTRAMOLECULAR IODOAMINATION} \\
\text{endo} & \quad \text{exo}
\end{align*}
\]