JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Iodine(III)-Mediated Intermolecular Allylic Amination under Metal-Free Conditions

José A. Souto,[†] Debora Zian,[†] and Kilian Muñiz*[,†,‡]

[†]Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain
[‡]Catalan Institution for Research and Advanced Studies (ICREA), Pg. Lluís Companys 23, 08010 Barcelona, Spain

Supporting Information

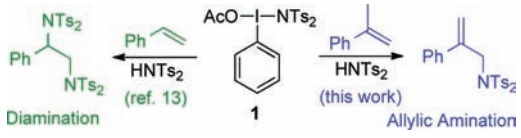
ABSTRACT: A new approach to direct intermolecular allylic amination has been developed using metal-free conditions at room temperature. The reaction employs a hypervalent iodine(III) reagent as an oxidant and bistosylimide as a nitrogen source. A series of different allylic aminations are presented with up to a 99% yield. Mechanistic studies including isotope labeling and Hammett correlation suggest that depending on the substrate structure two different mechanisms can be operating.

Allylic amines represent versatile building blocks for the synthesis of organic molecules of higher complexity. Direct allylic amination reactions functionalizing C−H bonds constitute an attractive single-step approach to this compound class. Such C−H activation processes traditionally require the use of metal promoters.[1,2] Reactions of this type have been developed using the powerful methodology of metal catalyzed nitrenoid insertion into allylic C−H bonds,[3] metal catalyzed C−H activation followed by nucleophilic additions of anionic nitrogen sources,[4] or application of aza-Wacker reactions.[5] Both intra- and intermolecular reaction pathways have become available for these elegant metal-mediated allylic amination reactions.

With the introduction of a selenium reagent, an early exception was described by Sharpless.[6] In addition, other metal-free amination processes involving formal C−H activation have recently evolved as an attractive synthetic alternative to metal-mediated reactions.[7] These reactions proceed under mild conditions, are safe to handle, and do not pose major toxicity problems. In particular, hypervalent iodine(III) reagents[8] have enabled the development of unique amination reactions such as carbazole synthesis[9,10] and direct aromatic and benzylic amination,[11,12] respectively.

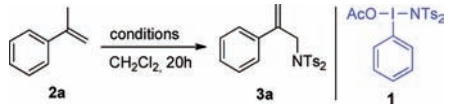
We have recently introduced the mixed hypervalent iodine reagent PhI(OAc)NTs_2 (**1**) and described its use in unprecedented intermolecular diamination reactions (Scheme 1, left pathway).[13,14] We herein describe a new metal-free allylic amination employing a hypervalent iodine(III) reagent that falls into this category (right pathway).

Scheme 1. Alkene Oxidation with 1: Diversification



A study on the oxidation of α-methyl styrene **2a** with iodosobenzene diacetate and bistosylimide did not undergo the expected diamination, but gave rise to an unexpected oxidation product, which was identified as the allylic amination product **3a**. Optimization of the reaction was straightforward and provided conditions that enable the selective oxidation of **2a** to **3a** in high yield (Table 1). Coinciding with an earlier observation,[13] dichloromethane represents the best solvent for oxidation with **1** and reactions proceed readily at room temperature. Most importantly, use of the preformed reagent **1** alone was not sufficient (entry 2). Addition of a catalytic amount of additional imide showed an effect (entry 3), and an equimolar combination of **1** and bistosylimide significantly enhanced the yield (entry 4). Finally, in the presence of 1.4 equiv of oxidant **1** complete conversion took place leading to an isolated yield of 87% for **3a** (entry 5). The reaction is very robust and was routinely conducted on a 5-mmol scale. It adds to the recent development of metal-free amination reactions of C−H bonds.[9−12]

Table 1. Discovery and Optimization of Metal-Free Allylic Amination



entry	conditions	yield [%][a]
1	PhI(OAc)$_2$ (1.2 equiv), HNTs$_2$ (2.4 equiv), 25 °C	45
2	**1** (1.1 equiv), 25 °C	50
3	**1** (1.1 equiv), HNTs$_2$ (0.2 equiv), 25 °C	54
4	**1** (1.1 equiv), HNTs$_2$ (1.2 equiv), 25 °C	62
5	**1** (1.4 equiv), HNTs$_2$ (1.5 equiv), 25 °C	87

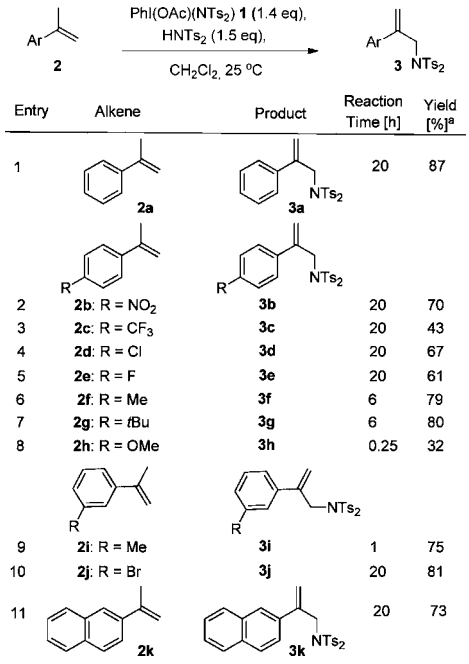
[a]Isolated yield after purification.

Under the optimized conditions a series of different α-methyl styrenes **2** were submitted to provide the corresponding allylic amination products **3** in good to excellent yields. These reactions proceed readily at room temperature, and quantitative conversion is obtained in less than 24 h. Common substituents are all tolerated by the procedure. Different substitution patterns include *para*-substitution (Table 2, entries 2−8),

Received: February 9, 2012
Published: April 16, 2012

dx.doi.org/10.1021/ja3013193 | J. Am. Chem. Soc. 2012, 134, 7242−7245

Table 2. Metal-Free Allylic Amination of α-Methyl Styrenes



Entry	Alkene	Product	Reaction Time [h]	Yield [%][a]
1	2a	3a	20	87
2	2b: R = NO_2	3b	20	70
3	2c: R = CF_3	3c	20	43
4	2d: R = Cl	3d	20	67
5	2e: R = F	3e	20	61
6	2f: R = Me	3f	6	79
7	2g: R = *t*Bu	3g	6	80
8	2h: R = OMe	3h	0.25	32
9	2i: R = Me	3i	1	75
10	2j: R = Br	3j	20	81
11	2k	3k	20	73

[a]Isolated yield after purification.

meta-substitution (entries 9,10), and a naphthyl derivative (entry 11). Attempts to carry out the corresponding allylic amination of 2-bromo α-methyl styrene led to less than 10% conversion over a period of 48 h. Electron-donating substituents were found to proceed at a higher rate, and in the case of 4-methoxy α-methyl styrene, complete conversion was obtained after 15 min. Unfortunately, product **3h** was found to be rather unstable leading to significant degradation during isolation and purification, which resulted in a low isolated yield (entry 8). In all other cases, the obtained products **3** are stable compounds, which due to the bissulfonimide group display high crystallinity.

For related iodine(III)-mediated C−H amination reactions, radical pathways were postulated.[9−12] In our case, a control experiment showed that the presence of *N*-*tert*-butyl-α-phenylnitrone, a radical trap compatible with iodine(III) reagents,[9] does not affect the conversion of **2a** to **3a**.[15] Another experiment with selectively deuterated **2a-d$_3$** gave rise to the corresponding bisdeuterated product **3a-d$_2$** (Figure 1). The

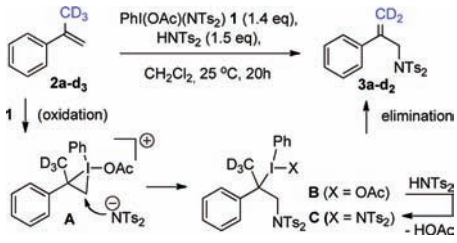
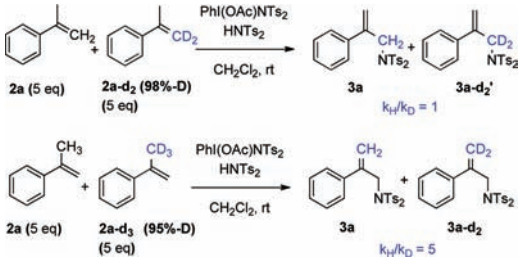


Figure 1. Mechanistic proposal.

observation of a selectively deuterated product excludes a potential radical abstraction mechanism. Instead, the present allylic oxidation of compounds **2** proceeds under double bond isomerization. We postulate a mechanism that starts with the formation of a iodo(III)cyclopropane **A**[14g,16] followed by regioselective opening at the more accessible terminal methylene position. Protonolysis of the iodine-acetate bond in **B** from free bistosylimide generates an intermediate **C** with pronounced electrophilicity at iodine. At this stage, the presence of the tertiary carbon center prevents diamination through nucleophilic substitution. Instead, subsequent elimination gives rise to the final product **3a-d$_2$** with correct deuterium labeling (Figure 1). Making use of deuterium labeling, two competition experiments were employed to further elucidate the mechanistic context (Scheme 2). First, a

Scheme 2. Competition Experiments

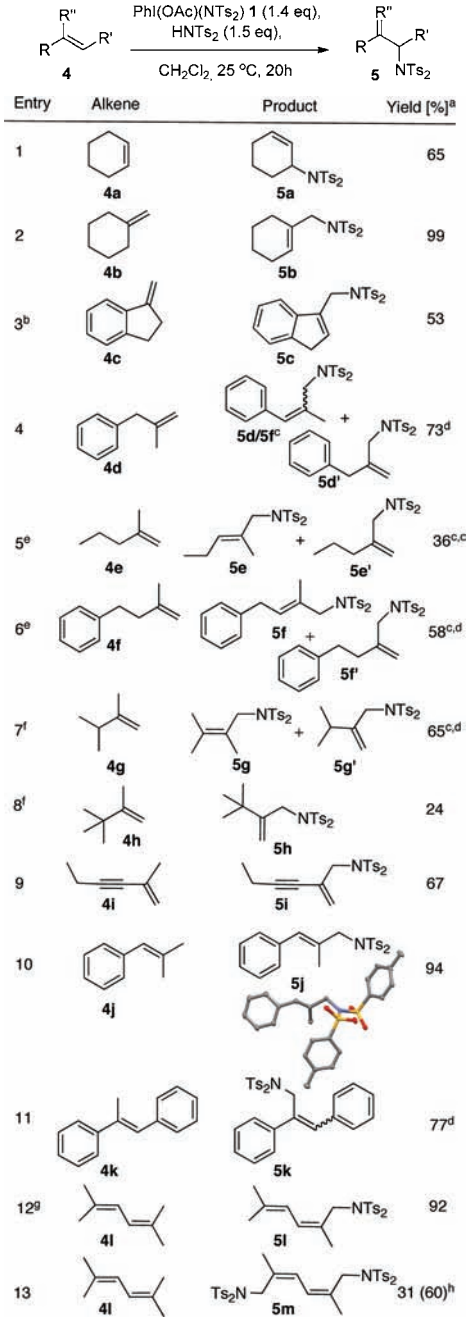


1:1 mixture of α-methyl styrene **2a** and its terminally bisdeuterated derivative **2a-d$_2$** were submitted to allylic amination. No secondary kinetic isotope effect was observed indicating that alkene coordination to the iodine reagent is rather fast and probably of a reversible nature. In contrast, for competition between **2a** and its deuterated methyl derivative **2a-d$_3$** a strong primary isotope effect k_H/k_D = 5 was observed, which is in agreement with expected values for a rate-determining elimination step,[17] and with the established leaving group character of the electrophilic iodine(III).[18] Such a postulated mechanism is in further agreement with a Hammett correlation study[15] employing α-methyl styrenes **2a,d−g**, which shows a moderate ρ-value of −1.5 and hence demonstrates enhanced reactivity for electron-rich arenes over the ones bearing electron-demanding substituents in the formation of the cationic intermediate arising from **C**.[19]

In addition to α-methyl styrenes the new allylic amination reaction proceeds readily with a series of other alkenes **4a−k** as well (Table 3). For example, cyclohexane **4a** gives rise to the selective formation of the corresponding allylic amine **5a** (entry 1). Exocyclic alkenes **4b** and **4c** undergo selective allylic amination to the corresponding products **5b,c**, the latter one with an exceptional rate (entries 2,3). The migration of the double bond into the ring is in agreement with the mechanistic proposal from Figure 1. For substrate **4d**, the existence of two different allylic C−H groups for elimination results in the formation of regioisomers **5d**/**5f** and **5d′** in a 3:2 ratio suggesting a preference for the benzylic position and therefore for products **5d**/**5f** with its conjugated double bond (entry 4). Related product mixtures of up to 3:1 were observed for gem-disubstituted alkenes **4e−g** (entries 5−7) demonstrating the requirement for regioselective opening of the initial iodocyclopropane. Even a *tert*-butyl-substituted alkene **4h** underwent clean amination (entry 8), although at a reduced rate due to steric congestion. As the only exception to the broad substrate scope so far, 2-methyl-2-hexene did only react at a low rate to give two isomeric allylic amides in an ∼10% yield.[15] Gratifyingly, for substrate **4i**, an exclusive preference for allylic amination over the potential formation of a propargylic amine was observed and amine **5i** was the only obtained oxidation product (entry 9). The trisubstituted styrene **4j** led exclusively to allylic amination

dx.doi.org/10.1021/ja3013193 | J. Am. Chem. Soc. 2012, 134, 7242−7245

Table 3. Metal-Free Allylic Amination: Substrate Scope



[a]Isolated yield after purification. [b]5 min reaction time. [c]Ratio **5d**/**5f** = 1/2; ratio **5e**/**5e**′ = 2/1; ratio **5f**/**5f**′ = 1/1; ratio **5g**/**5g**′ = 3/1. [d]Combined yield of isomers. [e]14 h reaction time. [f]10 h reaction time. [g]3 equiv of alkene, 12 h reaction time. [h]Yield from crude reaction mixture in brackets.

product **5j**. This outcome is particularly interesting in view of the earlier observation of selective diamination for the related case of *β*-methyl styrene.[13] Methylated stilbene **4k** underwent allylic amination as well. Here, the reaction gives rise to selective allylic amination in 77% yield, but proceeds with formation of two isomeric double bonds of the final stilbene **5k** [(*Z*)/(*E*) = 1/2.5] (entry 11). 1,3-Diene **4l** undergoes rapid allylic amination. In order to achieve monoamination to **5l**, an excess of the substrate was employed and the expected product was isolated in 92% yield (entry 12). Using a 1:3 ratio of **5l** and oxidant **1**, bisaminated product **5m** was obtained as the only product in 60% yield according to the ^{1}H NMR spectrum of the crude reaction mixture. This observation suggests that the second allylic amination on **5l** is faster than the initial one with **4l**. Purification of product **5m** was found to be difficult due to instability; however, a reasonable yield of 31% could be isolated (entry 13).

The latter examples show that, under certain conditions, allylic amination proceeds without double bond migration. For product **5j**, structural assignment was further assured through an X-ray crystallographic analysis.[15] The operating mechanism for this reaction is suggested to start from an interaction between the iodine(III) reagent **1** and the alkene in **4j** (Figure 2).

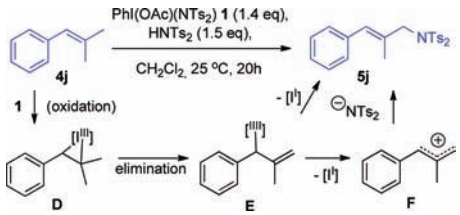


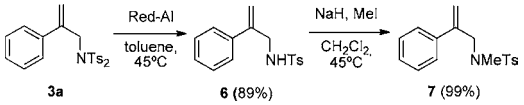
Figure 2. Mechanistic proposal for amination of **4f**.

For the resulting intermediate **D**, nucleophilic ring opening would require S_N2 reactions at a neopentylic or a quaternary position, respectively. As a consequence, elimination to **E** is believed to take place at this stage followed by either direct S_N2' reaction or via an allylic cationic intermediate **F** to give the thermodynamic product **5j**.

These latter results prove that reactions without double bond migration are equally feasible under the conditions of this new metal-free allylic amination. Hence, depending on the substrate structure, the reaction provides remarkable mechanistic flexibility.

To demonstrate the successful posterior manipulation of the sulfonyl groups at nitrogen, product **3a** was submitted to deprotection with Red-Al in toluene. Clean removal of one tosyl group to monosulfonylated **6** was observed, and upon methylation under standard conditions, quantitative formation of **7** was obtained (Scheme 3). This compound has been reported as a precursor to several potent herbicides.[20]

Scheme 3. Deprotection sequence



In summary, we have described conditions for new metal-free direct allylic amination reactions. The reaction is operationally simple using only the defined hypervalent iodine(III) **1** as a reagent and bistosylimide as a nitrogen source. It proceeds under mild conditions, and a range of substituents and functional groups are tolerated. Two mechanistically different pathways have been identified to operate within this new transformation, enabling an attractive allylic amination of a series of substrates.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental details and characterization data for new compounds, including CIF file on the X-ray crystallographic

dx.doi.org/10.1021/ja3013193 | J. Am. Chem. Soc. 2012, 134, 7242−7245

analysis of **5j**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

kmuniz@iciq.es

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the ICIQ Foundation and by the Spanish Ministerio de Economía y Competitividad (CTQ2011-25027).

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