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Catalytic Intermolecular Haloamidation of Simple Alkenes with *N*-Halophthalimide as Both Nitrogen and Halogen Source

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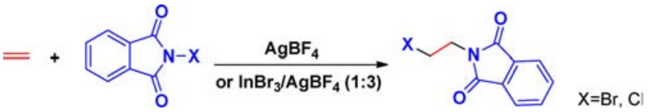
ABSTRACT



A simple, efficient, and highly atom economic haloamidation of simple alkenes has been developed, using $AgBF_4$ or $InBr_3/AgBF_4$ (1:3) as catalyst and *N*-halophthalimide as both nitrogen and halogen source. A broad range of olefins can be applied to afford vicinal haloamines in good yields and with high regioselectivity and diastereoselectivity.

Haloamidation of olefins is a fundamental transformation to produce vicinal haloamines as versatile synthons in organic synthesis.[1] Hence, the reaction has been extensively explored and remains a current research focus in order to address the remaining issues such as limited substrate scope and lack of enantiocontrol.[2] Typically, a haloamidation reaction occurs via nucleophilic attack to a halogenium intermediate with an amide nucleophile. In this step, the nucleophile is normally an externally added amide (Scheme 1).[3] The in situ generated amide anion derived from the *N*-halogenic reagents after delivering the halogenium ion may also participate in the nucleophilic addition, and this process is highly atom economic since both of the halogen and nitrogen moiety are preserved in the haloamidation product. Unfortunately, successful examples on such atom-economic processes are quite limited, presumably due to the low nucleophilicity of the in situ formed amide anion, a prerequisite for a high electrophilic halogenium ion.

In the catalytic haloamidation reaction, both Lewis acids[4] and Lewis bases[5] have been reported to facilitate smooth transformation by promoting the halogenium ion formation.[6] In this regard, notable progress has been achieved in intermolecular haloamidation of electron-deficient alkenes by Li et al.[7] Elegant catalytic asymmetric

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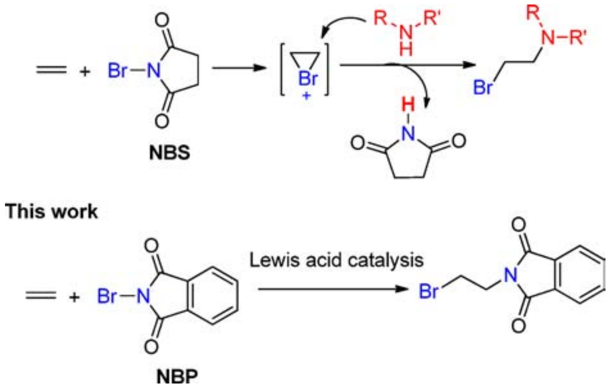
versions have recently been realized with $\mathrm{Sc(OTf)_3}$ and chiral *N*,*N*′-dioxide ligands by Feng et al.[8,9] As for the reactions with electron-neutral alkenes,[10] success has been mainly achieved with Ritter-type processes, wherein nitriles serve as the nucleophiles.[5d,11] Herein, we disclose a Lewis acid catalyzed intermolecular haloamidation of simple alkenes with *N*-halophthalimide as both nitrogen and halogen source under mild conditions.

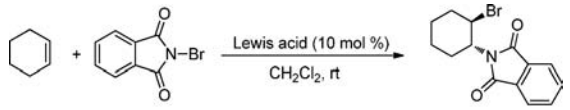
Scheme 1. Intermolecular Bromoamidation



Previously, Skell et al. have developed a photopromoted haloamidation reaction with *N*-bromophthalimide (NBP) as both nitrogen and bromine source.[12] However, this photoprotocol is of rather poor productivity and hence narrow substrate scope. To develop a mild and broadly applied haloamidation process for simple alkenes, we endeavored to employ NBP in the Lewis acid catalytic process. We reasoned that judiciously selected Lewis acid may facilitate bromonium formation via coordinating to the phthalimide moiety, and most importantly, the in situ generated phthalimide anion would have sufficient solubility and nucleophilicity to in situ participate in nucleophilic attack due to its benzo-conjugate nature. In addition, the use of phthalimide type halogenium reagents is also synthetically appealing as such *N*-protection moiety can be readily removed for subsequent transformations.[13]

Initially, cyclohexene **1a** was chosen as a model substrate with *N*-bromophthalimide as nitrogen/halogen source and this reaction was rather sluggish in the absence of catalyst even under light irradiation (Table 1, entries 1 and 2). To eliminate possible photocatalysis, all the screening and optimization were carried out in the dark with protection from light. An investigation on a series of metals identified Ag(I) and In(III) as the active metal Lewis acids (Table 1). In the presence of 5 mol % of $\mathrm{AgBF_4}$, the reaction proceeded smoothly to afford the desired product with 80% yield in 1.5 h (Table 1, entry 12). $\mathrm{In(BF_4)_3}$ (5 mol %), prepared in situ from $\mathrm{InBr_3}$ and $\mathrm{AgBF_4}$, is even a more active catalyst, and the reaction finished in 15 min to afford 87% yield of the desired product (Table 1, entry 14). In this case the catalyst loading can be reduced to 1 mol %, to afford the product with 70% yield in 1 h (Table 1, entry 16). The catalysis with Ag and In have also been conducted under light with similar results (Table 1, entries 13 and 15), suggesting the contribution from photocatalysis in the reactions under the present conditions, if present, should be minimal.

Table 1. Optimization for Intermolecular Haloamidation of Cyclohexene and *N*-Bromophthalimide[a]



1a **2a** **3a**

entry	Lewis acid	time (h)	yield[b] (%)
1	none	1.5	trace
2[e]	none	1.5	4
3	$\mathrm{Sc(OTf)_3}$	24	trace
4	$\mathrm{HfCl_4}$	24	trace
5	$\mathrm{FeCl_3}$	24	trace
6	$\mathrm{PdCl_2}$	24	trace
7	$\mathrm{AuCl_3}$	24	trace
8	$\mathrm{InBr_3}$	24	trace
9	$\mathrm{AgSbF_6}$	24	45
10	$\mathrm{AgNO_3}$	24	21
11	$\mathrm{AgBF_4}$	1.5	79
12[c]	$\mathrm{AgBF_4}$	1.5	80
13[c,e]	$\mathrm{AgBF_4}$	1.5	81
14[c]	$\mathrm{AgBF_4/InBr_3}$[f]	0.25	87
15[c,e]	$\mathrm{AgBF_4/InBr_3}$[f]	0.25	85
16[d]	$\mathrm{AgBF_4/InBr_3}$[f]	1	70

[a] The general reaction was carried out on a 0.1 mmol scale in 0.5 mL of $\mathrm{CH_2Cl_2}$, and the molar ratio of **1a**/**2a** is 1.5/1 in the dark. [b] Isolated yield. [c] 5 mol % catalyst loading. [d] 1 mol % catalyst loading. [e] Using 25 W household light. [f] The molar ratio of $\mathrm{AgBF_4/InBr_3}$ is 3/1.

With the optimal protocol in hand, we then turned our attention toward the scope of the reaction. Cyclic alkenes such as 1,4-cyclohexadiene **1b**, aromatic cycloalkenes **1d**, and indenes **1e** and **1f** could be readily converted to the corresponding products in good yields with excellent diastereoselectivities (Scheme 2, **3a**,**b**,**d**–**f**). The reaction

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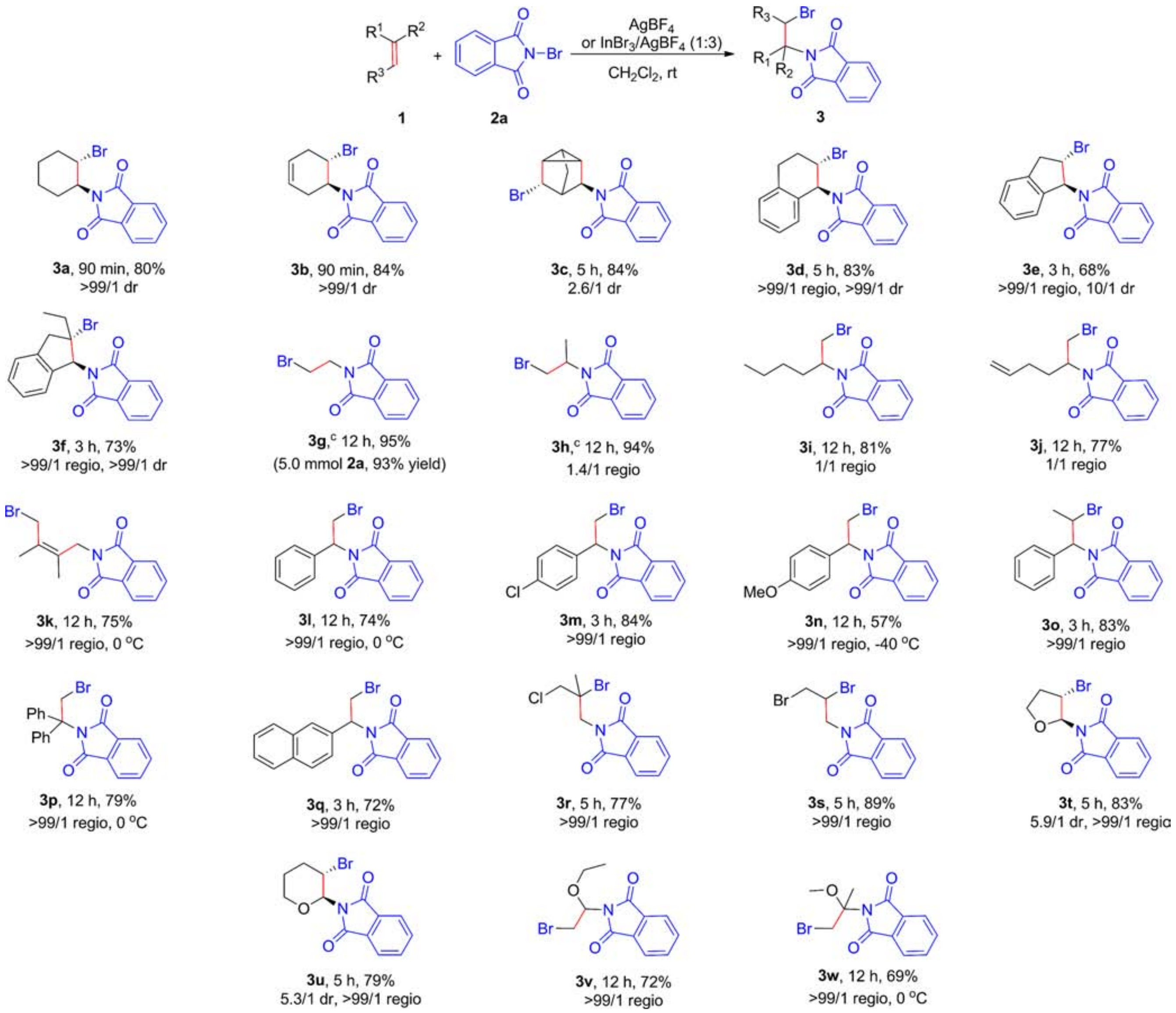
Scheme 2. Scope of Intermolecular Haloamidation of Alkenes and *N*-Bromophthalimide[a,b]



[a] The general reaction was carried out on 0.1 mmol scale in 0.5 mL CH_2Cl_2, and the molar ratio of **1a**/**2a** is 1.5/1, using $AgBF_4$ (5 mol %) as catalyst in the dark. [b] Isolated yield. [c] The reaction was carried out with 0.1 mmol **2a** and $InBr_3/AgBF_4$ (1:3) (5 mol %) with an alkene balloon in the dark.

with 2,5-norbornadiene **1c** also worked very well to give a rearranged bromoamidated adduct **3c** in high yield.

For acyclic alkenes, both styrenes and aliphatic alkenes can be applied to give Markonikov type adducts with good regioselectivity and in high yields (Scheme 2, **3g**–**q**). Styrenes bearing either electron-withdrawing group (Scheme 2, **3l**,**m**,**o**) or electron-donating substitutes (Scheme 2, **3n**) are equally applicable with the latter reaction requiring lower temperature to retard the polymerization. In particular, industrial olefins such as ethylene and propene can also be incorporated in the current catalysis. In these cases, $InBr_3/AgBF_4$ (1:3) was found to be better catalyst (Scheme 2, **3g** and **3h**), and a gram-scale reaction was illustrated in the reaction of ethylene with an ethylene balloon, showing similar results (Scheme 3, **3g**).

The reaction also worked well with functionalized alkenes such as allylic chloride/bromide (Scheme 2, **3r** and **3s**) and enol ethers (Scheme 2, **3t**–**w**). Acyclic dienes such as 2,3-dimethylbuta-1,3-diene have also been examined, giving 1,4-bromoamidated adduct **3k** in 75% yield, consistent of a delocalized allylic carbocationic intermediate.[14]

The reactions were next examined in terms of different *N*-halogenic reagents. *N*-Halogen succinimide such as NBS and NCS as the nitrogen/halogen source did not work. To our delight, the reactions with *N*-chorophthalimide proceeded smoothly with both cyclic and acyclic olefins

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(14) The reactions with electron-deficient alkenes such as chalcone have also been examined, showing no reaction.

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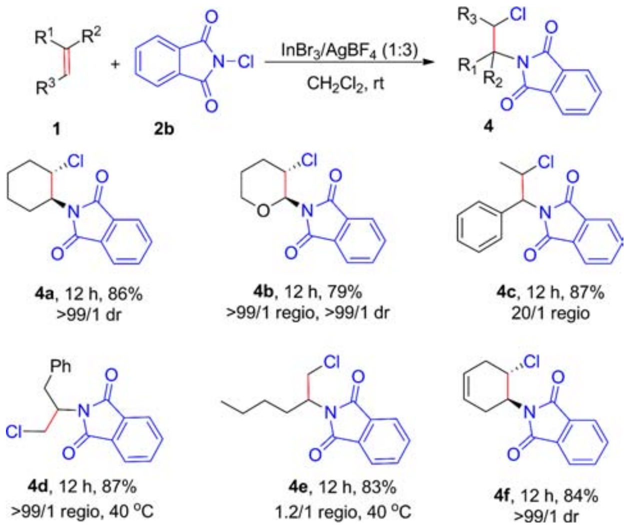
Scheme 3. Scope of Intermolecular Haloamidation with *N*-Chorophthalimide[a,b]

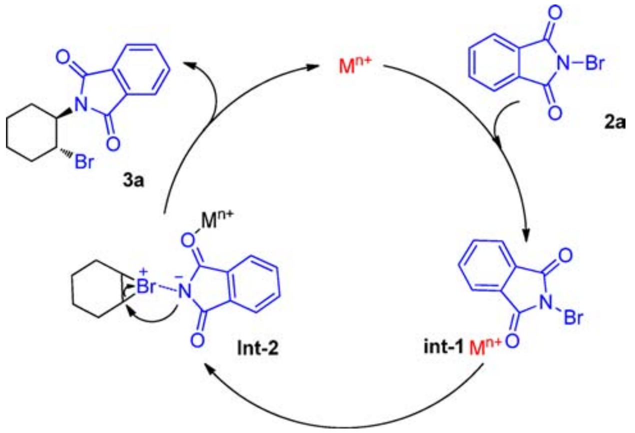


[a] The general reaction was carried out on a 0.1 mmol scale using $InBr_3/AgBF_4$ (1:3) (5 mol %) as catalyst in 0.5 mL CH_2Cl_2, and the molar ratio of **1a**/**2a** is 1.5/1 in the dark. [b] Isolated yield.

(Scheme 3). *N*-Fluorophthalimide has also been attempted, showing unfortunately no reaction.

Mechanistically, the reactions are proposed to occur via the typical halogenium intermediates (Scheme 4). In this scenario, Lewis acid promotes the generation of highly electrophilic halogenium ion by coordinating to the amide carbonyl group (**int-1**). A radical process involving phthalimide radical producing anti-Markovnikov products can not be totally excluded presently.[12,15] However, the observation of Markonikov products as well as cationic rearrangement products, e.g., **3c** and **3k**, are in support of the halogenium mechanism.

Scheme 4. Proposed Halogenium Ion Mechanism



In conclusion, we have developed a simple, efficient, and highly atom-economic haloamidation using *N*-halophthalimide as both nitrogen and halogen source. A broad range of olefins were tolerated including ethylene, propene, as well as other simple olefins, and the bromoamidation and chloroamidation products were obtained with good yields and high stereoselectivity.

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Supporting Information Available. Experimental procedures and ^1H and ^{13}C spectral data for compound **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.