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Lewis acid catalyzed intramolecular halo-arylation of tethered alkenes using *N*-halosuccinimide (NXS) as the halogen source: a general method for the synthesis of chromanones, chromans, quinolones, tetrahydroquinolines and tetralins

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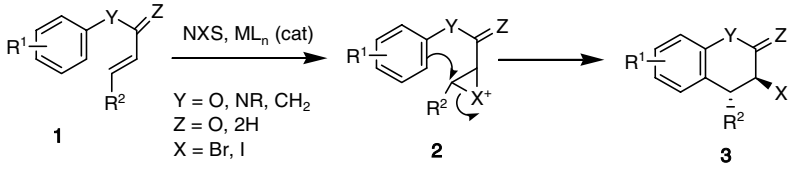
Abstract—Lewis acid catalyzed intramolecular halo-arylation of tethered alkenes was performed using *N*-halosuccinimide (NXS) as the halogen source. Among the Lewis acids investigated, $Sm(OTf)_3$ was found to be the best catalyst. This catalytic process provides a general method for the regio- and stereoselective synthesis of annulated arene heterocycles and carbocycles such as 2-chromanones, chromans, 2-quinolones, tetrahydroquinolines and tetralins possessing a halo-functionality.

Annulated arene heterocycles and carbocycles such as chromanones,[1] chromans,[2] quinolones,[3] tetrahydroquinolines[4] and tetralins[5] are present as important core structures in many biologically active natural products and pharmaceuticals. Intramolecular arylation of tethered alkenes offers a direct approach to construct these structural units. Other than intramolecular Heck reactions, catalytic intramolecular hydroarylation of alkenes either by arene-metalation Heck-type addition or by activation of alkenes are reported for the individual synthesis of different annulated arene compounds and these methods usually provide unfunctionalized annulated arenes.[6,7] More importantly, Barluenga has recently reported the IPy_2BF_4–HBF_4 promoted intramolecular iodoarylation of alkenes for the synthesis of tetralins, chromans and tetrahydroquinolines and also more complex polycyclic compounds via cascade cyclization.[8] We herein report our preliminary results on the Lewis acid catalyzed intramolecular halo-arylation of alkenes **1** using *N*-halosuccinimide (NXS) as the halogen source and the synthesis of the core structures of chromanones, chromans, quinolones, tetrahydroquinolines and tetralins possessing a halo-functionality **3**.

Current interest in our laboratory is to develop the catalytic and stereoselective 1,2-halo-functionalization of alkenes.[9] Accordingly, we anticipated that a suitable Lewis acid might catalyze the intramolecular haloarylation of alkenes **1** with NXS (Scheme 1) in line with Barluenga's work[8] on iodoarylation with IPy_2BF_4–HBF_4. In the search for an effective catalyst for the intramolecular haloarylation of alkenes with NXS, we



Scheme 1.

Keywords: Lewis acid; Catalyst; Halo-arylation; *N*-Halosuccinimide; Chromanones; Chromans; Quinolones; Tetrahydroquinolines; Tetralins.
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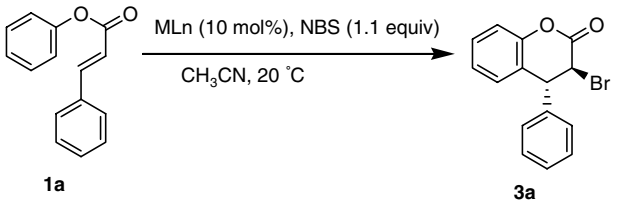
Table 1. Screening of Lewis acid catalysts for the intramolecular halo-arylation reaction of **1a** with NBS[a]



1a **3a**

Entry	ML_n	*t* (h)	Yield of **3a** (%)[b]
1	None	24	NR
2	$FeCl_3$	3	43
3	$CuCl_2$	3	28
4	$CoCl_2$	24	NR
5	$NiCl_2$	24	NR
6	$MnCl_2$	24	NR
7	$InCl_3$	30	36
8	$Zn(OTf)_2$	30	38
9	$La(OTf)_3$	30	25
10	$Y(OTf)_3$	30	70
11	$Yb(OTf)_3$	30	65
12	$Cu(OTf)_2$	3	78
13	$Sm(OTf)_3$	4	94 (90)

Yield in parentheses refers to the isolated yield of **3a**.
NR: No reaction.
[a] Lewis acid catalyzed haloarylation of **1a** was performed with 1.1 equiv of NBS and 0.1 equiv of Lewis acid in CH_3CN at 20 °C.
[b] Determined from the ^1H NMR spectra of the crude reaction mixture with naphthalene as internal standard.

screened different Lewis acids as catalysts for the intramolecular haloarylation of phenyl cinnamate **1a** with NBS. The results are depicted in Table 1. Lewis acids such as $FeCl_3$, $CuCl_2$, $Cu(OTf)_3$ and $Sm(OTf)_3$ showed moderate to good catalytic activity for the reaction of **1a** with NBS.

However, the $FeCl_3$ and $CuCl_2$ catalyzed reactions produced the desired product **3a** in poor yield along with a non-separable unidentified by-product. The metal triflate-catalyzed halo-arylation of **1a** yielded **3a** in good to excellent yield and among these $Sm(OTf)_3$ was found to be the best catalyst. It is noteworthy that substrate **1a** did not undergo any reaction with NBS in the absence of a Lewis acid (entry 1). When the substrate **1a** was treated with NBS (1.1 equiv) and $Sm(OTf)_3$ (0.1 equiv) in CH_3CN at 20 °C, it produced exclusively the 6-*endo* cyclized product **3a** in 90% yield (Table 1; entry 13).

We continued to investigate the scope of the catalytic method for the synthesis of other chromanones and chromans under the same conditions (Table 2). The aryl cinnamates **1b** and **1c** smoothly underwent $Sm(OTf)_3$-catalyzed intramolecular halo-arylation with NBS under the same reaction conditions and yielded the 3-bromochromanones **3b** and **3c** in 96% and 93% yields, respectively (Table 2; entries 1 and 2). The allyl aryl ethers **1d–h** did not give any cyclized product with NBS, but produced 3-iodochromans **3d–h** in moderate to good yields[10] with NIS (entries 3–7).

This methodology was further extended to synthesize nitrogenated heterocyclic compounds, such as quinolones and tetrahydroquinolines (Table 3). Both free as well as N-protected *N*-aryl cinnamic acid amides **1i–l** produced the quinolones **3i–l** with NBS in good to excellent yields (entries 1–4). In contrast, an *N*-protecting group proved to be essential for the halo-arylation of *N*-allyl anilines **1m–o** (entries 5–7). The compatibility of the halogen source (NXS) for the halo-arylation of N-protected-*N*-allylanilines depends on the nature of the alkenes.

Table 2. $Sm(OTf)_3$-catalyzed synthesis of 3-bromo-2-chromanones and 3-iodochromans

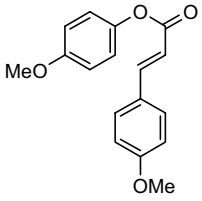
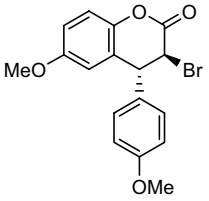
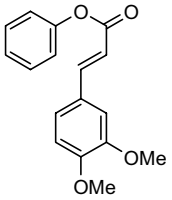
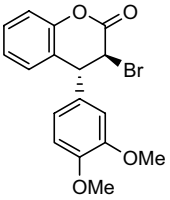
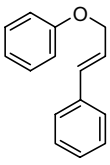
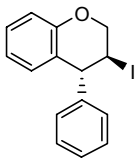
Entry	Substrate	NXS	*t* (h)	Product	Yield (%)
1	**1b** 	NBS	3	**3b** 	96
2	**1c** 	NBS	3	**3c** 	93
3	**1d** 	NIS	3	**3d** 	67

Table 2 (*continued*)

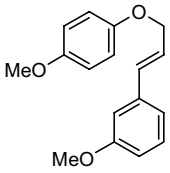
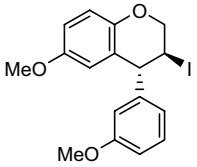
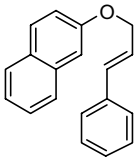
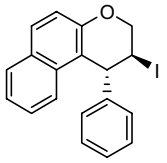
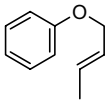
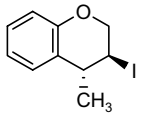
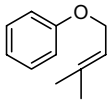
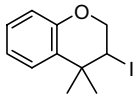
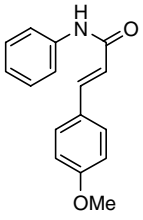
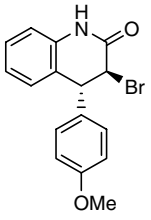
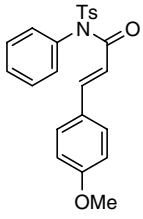
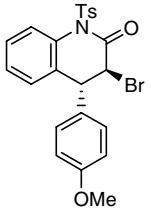
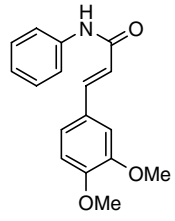
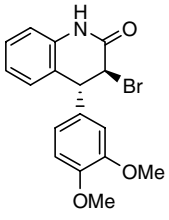
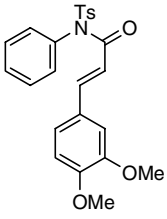
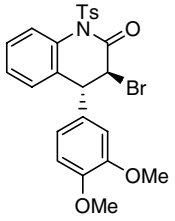
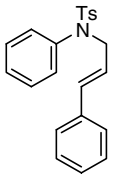
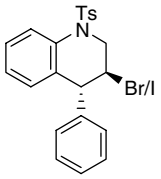
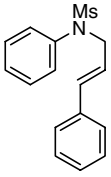
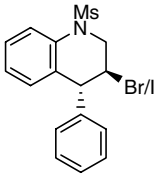
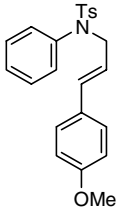
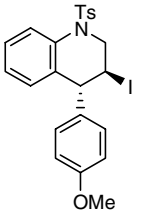
Entry	Substrate	NXS	*t* (h)	Product	Yield (%)
4	**1e** 	NIS	2.5	**3e** 	63
5	**1f** 	NIS	3	**3f** 	66
6	**1g** 	NIS	4.5	**3g** 	56
7	**1h** 	NIS	6	**3h** 	55

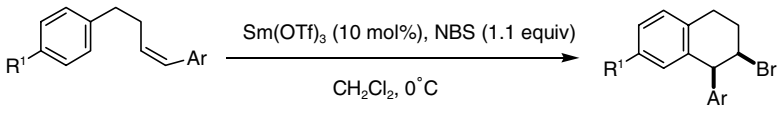
Table 3. $Sm(OTf)_3$-catalyzed synthesis of 3-bromo-2-quinolones and 3-halo-tetrahydroquinolines

Entry	Substrate	NXS	*t* (h)	Product	Yield (%)
1	**1i** 	NBS	3.5	**3i** 	85
2	**1j** 	NBS	4	**3j** 	94
3	**1k** 	NBS	3	**3k** 	89
4	**1l** 	NBS	3.5	**3l** 	93

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	NXS	*t* (h)	Product	Yield (%)
5	**1m** 	NBS NIS	3 3	***Br*-3m** ***I*-3m** 	67 64
6	**1n** 	NBS NIS	10 10	***Br*-3m** ***I*-3m** 	63 61
7	**1o** 	NIS	3	**3o** 	66



	R^1	Ar	t (h)	yield (%)
1p	H	Ph (*Z*/*E* 88:12)	1.5	82
1q	MeO	Ph (*Z*/*E* 88:12)	1	85
1r	H	4-$MeOC_6H_4$ (*Z*/*E* 90:10)	0.1	76
1s	MeO	4-$MeOC_6H_4$ (*Z*/*E* 90:10)	0.1	72

Scheme 2. Catalytic synthesis of tetralins.

Another relevant extension of this methodology is the synthesis of tetralin derivatives, these are also important key intermediates for the synthesis of pharmaceuticals.[5] Substrates **1p**–**s** smoothly underwent $Sm(OTf)_3$-catalyzed reaction with NBS at 0 °C in CH_2Cl_2 and gave the tetralin products **3p**–**s** in good yields (Scheme 2).

In summary, we have developed a Lewis acid catalyzed intramolecular halo-arylation of alkenes using inexpensive and easily available *N*-halosuccinimide (NXS) as the halogen source. This catalytic process is a regio- and stereoselective method and is utilized to synthesize a diverse range of structural motifs, for example, chromanones, chromans, quinolones, tetrahydroquinolines and tetralins with halo-functionality. A better understanding of this Lewis acid catalyzed intramolecular halo-arylation of tethered alkenes might provide a flexible catalytic and asymmetric method which we are currently investigating.

Acknowledgements

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10. No rearranged product as observed by Barluenga (Ref. 8a) was found.