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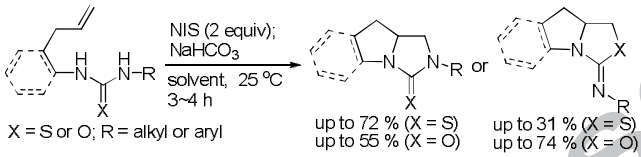

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Intramolecular aminochalcogenation and diamination of alkenes empolying *N*-iodosuccinimide

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ABSTRACT

A NIS-mediated intramolecular diamination and aminosulfuration of alkenes with *N*-alkyl or *N*-aryl thioureas is reported. A chiral cyclic thiourea was also synthesized by the methodology. The protocol is also proven to be efficient in the intramolecular diamination and/or aminooxygenation of alkenes with *N*-alkyl or *N*-aryl ureas and ones with *N*-carbamate sulfamides. The resulting bicyclic thiourea could be further transformed into bicyclic guanidine.

Vicinal diamines occur in a variety of bioactive molecules and natural products, and serve as building blocks in organic transformation, and chiral ligands for stereoselective synthesis.[1] Direct difunctionalization of alkenes is clearly an attractive route to generate vicinal diamines,[2] and, since 2005, much resurgent attention have been paid to the development of efficient catalytic procedures for Pd(II)-,[3] Cu(II)-,[4] Ni(II)-,[5] and Au(I)-mediated[6] intramolecular diamination of alkenes. Very recently, metal-free difunctionalization of alkenes have been also established to circumvent the toxicity and cost issue associated with metal catalysts. Muñiz et al. reported the intramolecular diamination and aminooxygenation of alkenes with *N*-sulfonyl ureas in the presence of iodonium reagent IPy_2BF_4 (Py = pyridine).[3] Widenhoefer et al. further employed *N*-iodosuccinimide (NIS) as an efficient promoter for the intramolecular diamination and alkoxyamination of alkenes with *N*-sulfonyl ureas.[7] Hennecke et al. also reported an intramolecular *anti*-selective diamination reaction of alkenes in the presence of NIS.[8] Recently, Muñiz et al. presented an intramolecular diamination of alkenes with *N*-Boc sulfamides and *N*-sulfonyl ureas employing bromide catalysis with sodium chlorite as oxidant.[9] Michael et al. reported an intramolecular aminooxygenation of alkenes with ureas using PhI=O and an acid promoter.[10] Wirth et al. also developed stereoselective aminooxygenation and diamination of alkenes using chiral $ArI(OAc)_2$ /acid systems.[11] Chang et al. employed $PhI(OAc)_2$ and a halide additive to improve the intramolecular diamination of alkenes with *N*-sulfonyl ureas.[12]

However, most employed alkene substrates in these processes are those having a *N*-sulfonyl, or *N*-carbamate group, and, in the case of ones with *N*-alkyl or *N*-aryl ureas and sulfamides, excess metal oxidant, high temperature and extended reaction time are required to achieve considerable yields for the diamination of alkenes (a, Scheme 1).[4] Metal-free methods for intramolecular diamination of alkenes with *N*-alkyl or *N*-aryl ureas are still rare, and often suffered from the formation of aminooxygenation products and poor yield. (b, Scheme 1).[7,11]

As an important vicinal diamine derivatives, imidazolidine-2-thiones have been reported to exhibit a diverse range of biological and pharmaceutical activities,[13] represent excellent ligands in bioactive coinage metal complexes,[14] and serve as important precursors for the synthesis of guanidines.[15] Although a variety of functional groups were used as nitrogen sources for oxidative difunctionalization of alkenes, thioureas haven't been employed for this process yet. As part of our ongoing interest in the development of new methodology for the synthesis of cyclic vicinal diamines and their application in catalysis,[16] herein we first report a NIS-mediated intramolecular diamination and aminosulfuration of alkenes with *N*-alkyl or *N*-aryl thioureas (c, Scheme 1). The protocol is also applied successfully to the oxidative difunctionalization of those with *N*-alkyl or *N*-aryl ureas and *N*-carbamate sulfamides.

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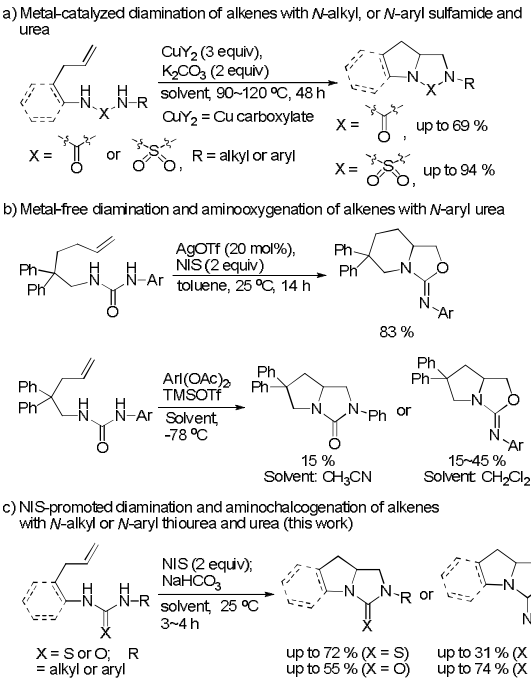
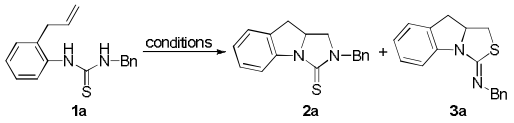


Scheme 1. Intramolecular diamination of alkenes with *N*-alkyl or *N*-aryl substrates

Bromine and iodine reagents are often used to activate and oxidize alkene through the formation of halonium ions. We started our investigation with reacting halogen reagents with the difunctionalization of *N*-alkenyl thiourea **1a** (Table 1). Among common used iodine reagent, NIS exhibited the most activity to promote this process to afford a mixture of diamination product **2a** and aminosulfuration product **3a** with low selectivity (Table 1, entry 1). Other iodine reagents such as Py_2IBF_4 and $PhI(OAc)_2$/TMSOTf led to disappointing results (Table 1, entries 2 and 3), though they were efficient promoters under same reaction conditions towards other intramolecular difunctionalizations of alkenes.[3d,11] Adding $NaHCO_3$ (1 equiv) as base led to an improved total yield towards diamination and aminosulfuration (Table 1, entry 4). Using NBS, almost no formation of alkene difunctionalization product could be observed (Table 1, entry 5). Lowering the reaction temperature to -30 °C led to a decreased yield (Table 1, entry 6), and reducing the amount of NIS to 1.5 equiv resulted in significant decrease in reaction yield (Table 1, entry 7). Using either CH_2Cl_2 or THF as a solvent led to poor yields (Table 1, entries 8 and 9).

Table 1. Intramolecular diamination and aminosulfuration of thiourea **1a**[a]



Entry	Reagent (equiv)	Base (1 equiv)	Solvent Toluene	Yield (%)[b]	
				2a	**3a**
1	NIS (2.0)	–	Toluene	29	19
2	Py_2IBF_4 (1.5)	–	Toluene	0	10
3[c]	$PhI(OAc)_2$ (2.0) TMSOTf (1.0)	–	CH_2Cl_2	2	3
4	NIS (2.0)	$NaHCO_3$	Toluene	34	22
5	NBS (2.0)	$NaHCO_3$	Toluene	0	4
6[d]	NIS (2.0)	$NaHCO_3$	Toluene	15	24
7	NIS (1.5)	$NaHCO_3$	Toluene	5	11
8	NIS (2.0)	$NaHCO_3$	CH_2Cl_2	0	23
9	NIS (2.0)	$NaHCO_3$	THF	25	12

[a] Reaction conditions: Solvent, 0~25 °C, 4 h. [b] Isolated yields. [c] -78~25 °C. [d] -30 °C.

Under optimized condition, the generality and scope of this synthetic protocol were investigated (Table 2). Different from *N*-2-allylphenyl thiourea **1a**, *N*-pentenyl thioureas **1b~1d** with a second *N*-alkyl substituent were cyclized to afford cyclic thioureas **2b~2d** as an only product with moderate yields (40~72%), respectively (Table 2, entries 2~4). Notably, upon treatment with NIS, thiourea **1c** having a chiral auxiliary could be cyclized to form the diastereomeric products (*S*, *S*)-**2c** and (*R*, *S*)-**2c** as a mixture with moderate diastereoselectivity (75:25 dr) (Table 2, entry 3). The diastereomers (*S*, *S*)-**2c** and (*R*, *S*)-**2c** can be easily separated by recrystallization. The absolute configuration of (*S*, *S*)-**2c** was confirmed by the X-ray diffraction analysis of its single crystals (Figure 1).[17] The chiral auxiliary methodology affords an efficient method for synthesis of chiral cyclic thiourea. Contrary to **1b~1d**, *N*-pentenyl thioureas **1e~1g** with a second *N*-aryl substituent were cyclized to afford 2-aminothiazoline thioureas **3e~3g** as an only product with low yields (15~31%), respectively (Table 2, entries 5~7). Either electron-deficient substituent (4-CF_3) or electron-donating group (4-OMe) was tolerated towards the process. We further examined the reactivity of NIS towards the alkene difunctionalization with *N*-alkyl or *N*-aryl ureas **4a~4d**. Due to the low solubility of **4a~4d** in toluene, we carried out the reactions in MeCN. Upon treatment with NIS, **4a~4d** were cyclized with good to excellent total yields (63~98 %), respectively (Table 2, entries 8~11). Aminooxygenation product **6a** was obtained as an only product in the cyclization of *N*-2-allylphenyl urea **4a** (Table 2, entry 8). Reaction of *N*-2-allylphenyl urea **4b** with NIS also predominately gave the aminooxygenation product **6b**, with diamination product **5a** isolated as a minor compound (Table 2, entry 9). Under the reaction condition, both *N*-pentenyl ureas **4c** and **4d** gave the corresponding aminooxygenation products and diamination products in high total yields (86~96 %) but low selectivity (Table 2, entries 10 and 11).

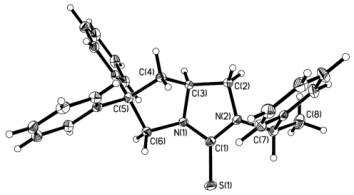
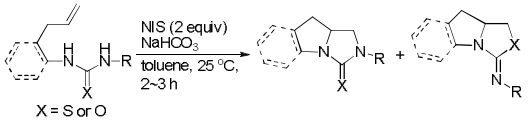
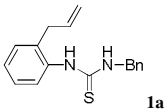
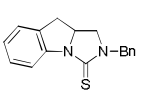
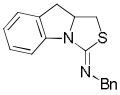
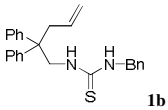
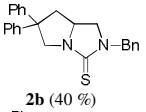
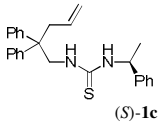
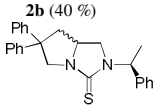
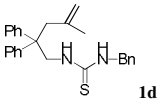
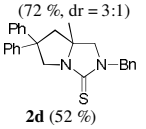
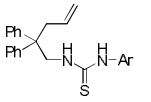
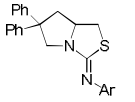
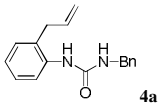
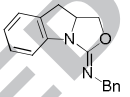
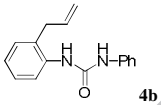
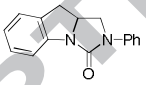
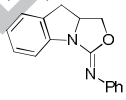
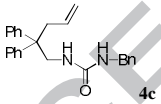
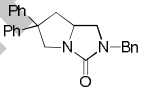
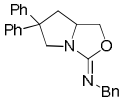
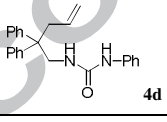
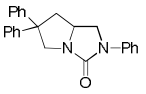
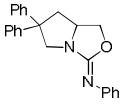


Figure 1. Molecular structure of (*S*,*S*)-**2c**.

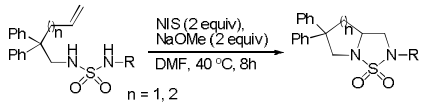
Table 2. Intramolecular Aminochalcogenation and Diamination of Thioureas and Ureas[a]



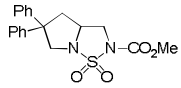
entry	Starting Material	Product[b]	
1	 **1a**	 **2a** (34 %)	 **3a** (22 %)
2	 **1b**	 **2b** (40 %)	
3	 (*S*)-**1c**	 (*S*,*S*)-**2c**/(*R*,*S*)-**2c** (72 %, dr = 3:1)	
4	 **1d**	 **2d** (52 %)	
			
5	Ar=Ph, **1e**		**3e** (15 %)
6	Ar = 4-$CF_3C_6H_4$, **1f**		**3f** (31 %)
7	Ar = 4-$OMeC_6H_4$, **1g**		**3g** (15 %)
8	 **4a**		 **6a** (63 %)
9	 **4b**	 **5b** (24 %)	 **6b** (74 %)
10	 **4c**	 **5c** (38 %)	 **6c** (48 %)
11	 **4d**	 **5d** (55 %)	 **6d** (41 %)

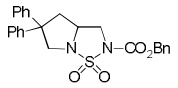
[a] Reaction conditions: NIS (2 equiv), Solvent (toluene as solvent for **1a~1g**; acetonitrile as solvent for **4a~4d**), $NaHCO_3$ (1 equiv), 0~25 °C, 2~3 h. [b] Isolated yields.

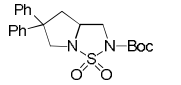
Chart 1. Intramolecular Diamination of Sulfamides[a][b]

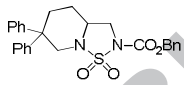


7 **8**

 **8a** (84 %)

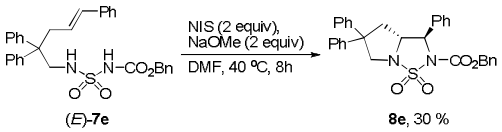
 **8b** (77 %)

 **8c** (89 %)

 **8d** (90 %)

[a] Reaction conditions: NIS (2 equiv), NaOMe (2 equiv), DMF, 40 °C, 8 h. [b] Isolated yields.

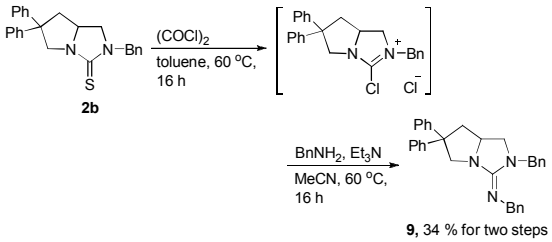
Muñiz et al. recently presented a KBr-catalyzed intramolecular diamination of alkenes with *N*-carbamate sulfamides using sodium chlorite as oxidant in the presence of NaOAc as base.[9] We also tested our methodology in the process, and NIS was proven to be an efficient promoter towards the process (Chart 1). In the presence of 2 equiv NIS and NaOMe as a base, methyl, benzyl, and *tert*-butyl substituted N-carbamate sulfamides were successfully transformed into the corresponding dicyclic sulfamides **8a~8c** in good yields (77~89 %), respectively. Notably, the 6-membered ring sulfamide **8d** could also be prepared in high yield of 90 % through the methodology.



(*E*)-**7e** **8e**, 30 %

Scheme 2. Diamination of internal alkene

An experiment was carried out to investigate the mechanism of the two C-N bond-forming steps in the NIS-promoted intramolecular diamination of alkenes with *N*-carbamate sulfamides (Scheme 2). Treatment of (*E*)-**7e** with NIS offered *anti*-configured **8e** as a single diastereoisomer, indicating that the process is stereospecific regarding the double bond geometry. The result also proved the new methodology to be compatible with internal alkenes.



2b **9**, 34 % for two steps

Scheme 3. Synthesis of cyclic guanidine from bicyclic thiourea

Cyclic guanidines are widely present in a variety of the marine natural products,[18] and used as organocatalysts,[19] ligands in metal complexes,[20] and powerful organic bases.[21] Using a literature method,[15] chlorination of cyclic thiourea **2b** with oxalyl chloride

could afford intermediate imidazolidinium salt, which was treated with benzylamine to offer a desired guanidine **9** (Scheme 3).

In conclusion, we present a NIS-mediated intramolecular diamination and aminosulfuration of alkenes with *N*-alkyl or *N*-aryl thioureas. A chiral cyclic thiourea was also synthesized by the methodology. The protocol was further submitted to the oxidative difunctionalization of alkenes with *N*-alkyl or *N*-aryl ureas and those with *N*-carbamate sulfamides. The resulting bicyclic thiourea could be readily converted into bicyclic guanidine. The methodology provides efficient way for the facile syntheses of bicyclic thioureas, ureas, and guanidines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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Intramolecular Aminochalcogenation And Diamination of Alkenes Empolying *N*-iodosuccinimide

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A NIS-mediated intramolecular diamination and aminosulfuration of alkenes with N-alkyl or N-aryl thioureas has been developed, which is also proven to be efficient in the intramolecular diamination and/or aminooxygenation of alkenes with N-alkyl or N-aryl ureas and ones with N-carbamate sulfamides.