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$InBr_3$ Catalyzed intermolecular hydroamination of unactivated alkenes

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Abstract—$InBr_3$ has been demonstrated to be a simple catalyst for the intermolecular hydroamination of unactivated alkenes to produce tosyl- and mesyl-protected amines in moderate to good yields.

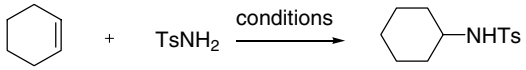
Hydroaminaion of alkenes to form saturated carbon–nitrogen bond is an atom-economical and efficient way to synthesize many nitrogen containing compounds.[1] Thus far, catalytic intermolecular hydroamination of unactivated alkenes remains an important and challenging strategy, and only a few examples are known.[2]

The previous work in our group had showed that some Indium(III) compounds were very active in many organic transformations.[3] Here we provide the first examples of In(III) bromide catalyzed intermolecular hydroamination of unactivated alkenes.

The readily available *p*-toluenesulfonamide and cyclohexene were used for preliminary study. The effects of various Indium(III) compounds to catalyze the hydroamination reaction were investigated (Table 1).

As we can see from Table 1, $InBr_3$ stood out to be an excellent catalyst for this reaction. Other In(III) compounds, either were not active (entries 2–5) or gave lower yields (entries 6 and 7). Thus, *N*-cyclohexyl-*p*-toluenesulfonamide could be prepared in 92% isolated yield by reacting $TsNH_2$ with 4 equiv of cyclohexene in toluene with catalytic amount of $InBr_3$ (20 mol %) at 120 °C for 16 h. THF and mixtures of toluene with THF were found to be unsuitable as reaction solvents. Reducing the reaction time (from 16 h to 8 h, entry 9), and the amount of Lewis acid (from 20 mol % to 10 mol %, entry 10) resulted in decreasing yields.

Table 1. Intermolecular hydroamination with different indium(III) compounds as catalysts



Entry	Catalyst	Conditions[a]	Yield[b] (%)
1	—	120 °C, 60 h	0
2	$In(TFA)_3$	120 °C, 16 h	0
3	$In(TFacac)_3$	120 °C, 16 h	0
4	InF_3	120 °C, 16 h	0
5	$InF_3{\cdot}3H_2O$	120 °C, 16 h	<5
6	InI_3	120 °C, 16 h	39
7	$InCl_3$	120 °C, 16 h	88
8	$InBr_3$	120 °C, 16 h	92
9	$InBr_3$	120 °C, 8 h	69
10[c]	$InBr_3$	120 °C, 16 h	53
11	$InBr_3$	160 °C, 16 h	81
12	$InBr_3$	90 °C, 16 h	67

TFA = trifluoroacetate; TFacac = trifluoroacetylacetonate.
[a] Typical reaction conditions: *p*-toluenesulfonamide (1 mmol), cyclohexene (4 mmol), Lewis acid (0.2 mmol), toluene (2 mL), in a sealed tube. The temperatures listed in the table are oil bath temperatures.
[b] Isolated yield after purification by column chromatography.
[c] 10 mol % of catalyst was used.

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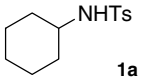
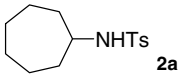
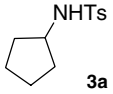
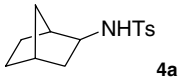
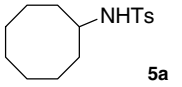
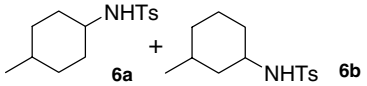
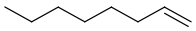
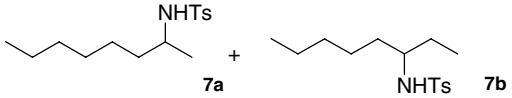
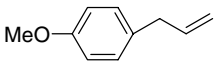
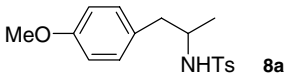
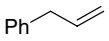
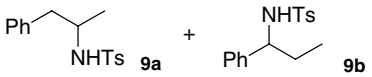
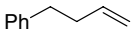
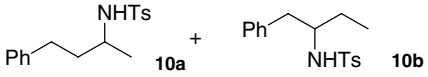
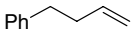
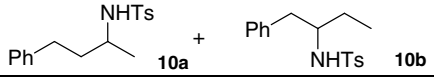
Meanwhile, changing the reaction temperature (from 120 °C to 160 °C, entry 11, from 120 °C to 90 °C, entry 12) afforded lower yields.

Next, we investigated the reactions with various alkenes using the optimal conditions stated above. The results are summarized in Table 2.[4] A range of different unactivated olefins was studied in the reaction. Cyclohexene, cycloheptene and cyclopentene gave the desired products in excellent yields (entries 1–3). For 4-methyl-cyclohexene, a mixture of 1- and 2-hydroamination (**6a**,**6b**) products were collected and **6a** was favored (entry 6) due to the less hindrance of 1,4 position. In the case of terminal olefins, Markovnikov addition products were observed (entries 7–11) and in these cases, usually two types of products were obtained: 2-hydroamination (**7a**–**10a**) and 3-hydroamination (**7b**–**10b**) products. The 3-hydroamination products (**7b**–**10b**) could be formed from an initial terminal double bond isomerization to an internal one followed by Markovnikov addition by *p*-toluenesulfonamide. The ratio of 2- and 3-hydroamination products varied with different

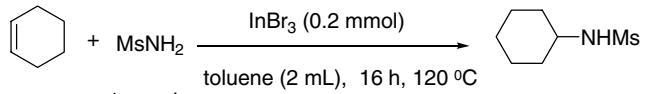
Table 2. Intermolecular hydroamination of *p*-toluenesulfonamide with various alkenes

Entry	Alkene	Product[a]	Yield[b] (%)
1		 **1a**	92
2		 **2a**	94
3		 **3a**	86
4		 **4a**	67
5		 **5a**	44
6		 **6a** **6b**	65 (77:23)[c]
7		 **7a** **7b**	78 (50:50)
8		 **8a**	78
9[d]		 **9a** **9b**	50 (94:6)
10		 **10a** **10b**	41 (70:30)
11[d]		 **10a** **10b**	60 (65:35)

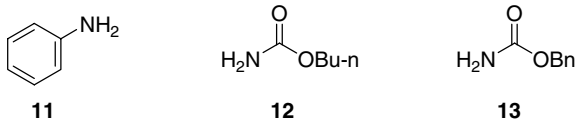
[a] Typical reaction conditions: *p*-toluenesulfonamide (1 mmol), olefins (4 mmol), Lewis acid (0.2 mmol), toluene (2 mL), in seal tube, 120 °C, 16 h.
[b] Isolated yield after purification by column chromatography.
[c] Ratio of the two isomers.
[d] Reaction run for 40 h.

terminal olefins. For allylbenzenes (entries 8 and 9), 3-hydroamination products were minimum as the internal olefins (prop-1-enylbenzenes), isomerized from the terminal olefins, could not furnish the desired hydroamination product under our conditions.

Noticeably, the reaction also worked well with alkylsulfonamides (Eq. 1). But with other nitrogen-based molecules, such as anilines (**11**) and carbamates (**12**, **13**), reactions gave no desired products.

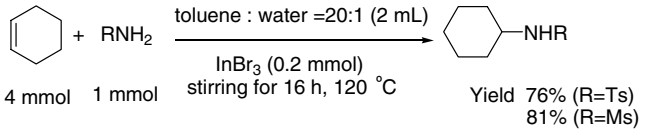


(1)

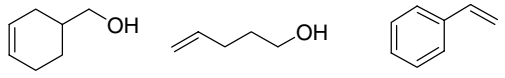


11 **12** **13**

It was interesting to note that this reaction also worked in the presence of small amount of water (Eq. 2). Unfortunately, the reactions with unprotected hydroxyl containing olefins (**14** and **15**) did not furnish the desired products. For styrene (**16**), a mixture of undeterminable polymerized products was observed.



(2)



14 **15** **16**

In summary, $InBr_3$ had been found to be a good catalyst for the intermolecular hydroamination of simple olefins to afford Markovnikov addition products. It is noteworthy that as an air and water stable Lewis acid, $InBr_3$ catalyzed the reaction in the presence of water. Further work is to explore the scope of the reaction, and stereoselective hydroamination using chiral Indium complexes[5] is also under investigation.

Acknowledgments

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References and notes

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4. *Illustrative experimental procedure (synthesis of N-cyclohexyl-p-toluenesulfonamide)*: To a 15 mL sealed tube was added *p*-toluenesulfonamide (171.2 mg, 1.0 mmol), cyclohexene (0.4 mL, 4.0 mmol), $InBr_3$ (70.8 mg, 0.2 mmol) and followed by toluene (2 mL). After shaking, the tube was sealed and heated in an oil bath at 120 °C. The reaction was left at this temperature for 16 h. After the sealed tube was slowly cooled to room temperature, the solvent was removed by Rotary Evaporator, and the residue was purified using flash silica gel chromatography to afford a product (231.8 mg, 92%); white solid; $R_f = 0.40$ (ethyl acetate/hexane = 1:4). FTIR (KBr) cm^{-1}: 3246, 3063, 3053, 2934, 2851, 2801, 1597, 1497, 1443, 1323, 1155, 1094, 989, 883, 816, 667, 575, 546; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, $J = 8.3$ Hz, 2H, Ph*H*), δ 7.31 (d, $J = 8.0$ Hz, 2H, Ph*H*), δ 4.30 (d, $J = 7.1$ Hz, 1H, N*H*), δ 3.23–3.09 (m, 1H, NHC*H*), δ 2.45 (s, 3H, PhCH_3), δ 1.82–1.73 (m, 2H, CH_2), δ 1.70–1.62 (m, 2H, CH_2), δ 1.33–1.08 (m, 6H, $3 \times$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 138.5, 129.6, 126.9, 52.6, 33.8, 25.1, 24.6, 21.5; HRMS Calcd for $C_{13}H_{19}NO_2S$ [M^+]: 253.1136. Found: 253.1105.
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