Recyclable Gallium as Catalyst Precursor for a Convenient and Solvent-Free Method for the Intermolecular Addition of Sulfonamides to Alkenes

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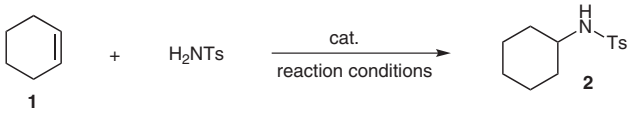
Abstract: Gallium(III) iodide, which is conveniently formed in situ from gallium and iodine, is a competent catalyst for the inter- and intramolecular addition of *p*-toluenesulfonamides to alkenes. After each reaction, the metallic gallium can easily be recycled and used for subsequent transformations.

Key words: alkenes, amines, gallium, hydroamination, sulfonamides

During the last few years, many metal complexes that catalyze the addition of NH across carbon–carbon multiple bonds have been identified and used for a wide range of so-called hydroamination reactions.[1] However, the fact that these reactions are usually performed under homogeneous conditions can be regarded as a severe drawback because catalyst recycling is difficult or even impossible, for example, in the case of highly sensitive catalysts like rare earth or group IV metal catalysts. As a consequence, most of the synthetic procedures published in the literature do not describe any catalyst recycling at all;[2] the catalysts are simply destroyed during the workup procedure and finally disposed. On the other hand, a number of easily recyclable heterogeneous hydroamination catalysts exist but they are usually rather limited in scope.[3] In order to develop a recyclable hydroamination catalyst that combines the advantages of both types of catalysts, we turned our attention towards an application of simple gallium(III) halides GaX_3 (X = Cl, Br, I) as hydroamination catalysts. Gallium(III) halides are regarded as soft Lewis acids and they are soluble in common organic solvents.[4,5] Consequently, they can be regarded as promising catalysts for the addition of less basic amine derivatives to alkenes because they are supposed to activate the alkene by π-complexation towards a nucleophilic attack of the less basic N-nucleophile. An additional interesting point is that gallium is a nontoxic metal that easily reacts with halogens at room temperature to give gallium(III) halides. Correspondingly, it is possible to generate the gallium halide in situ by a simple reaction of metallic gallium with the corresponding halogen (e.g., iodine).[6]

Initial reactions between cyclohexene (**1**) and *p*-toluenesulfonamide[3b,7] were carried out at 105 °C in sealed Schlenk tubes in the presence of catalytic amounts of commercially available $GaCl_3$ (Table 1). During this study, it was found that best results are obtained when the reaction is performed in the absence of a solvent with a 2:1 ratio between the alkene and *p*-$TsNH_2$. Corresponding reactions, performed for 16 hours or 2 hours with 5 mol% of $GaCl_3$ gave the desired sulfonamide **2** in 94% and 86% yield, respectively (Table 1, entries 7 and 8). Additional reactions performed for 2 hours under comparable condi-

Table 1 Addition of *p*-Toluenesulfonamide to Cyclohexene (**1**) in the Presence of Various Gallium Catalysts



1 **2**

Entry	Catalyst	mol%	Alkene/ $TsNH_2$ ratio	Solvent[a]	Temp (°C)	Time (h)	Yield **2** (%)[c]
1[a]	$GaCl_3$	24	1.2:1	toluene	105	24	92
2[a]		24	1.2:1	1,4-dioxane	105	24	<5
3[a]		24	1.2:1	THF	105	24	<5
4[a]		24	1.2:1	DCE	105	24	65
5[a]		12	1.2:1	toluene	105	24	67
6[a]		6	1.2:1	toluene	105	24	55
7[b]		5	2:1	–	105	16	94
8[b]		5	2:1	–	105	2	86
9[b]	$GaBr_3$	5	2:1	–	105	2	84
10[b]	GaI_3	5[d]	2:1	–	105	2	96
11[b]		5[d]	2:1	–	105	1	83
12[b]		1[e]	2:1	–	105	21	5
13[b]		5[d]	2:1	–	90	2	12
14[b]	Ga	5	2:1	–	105	16	<5
15[b]	I_2	7.5	2:1	–	105	16	<5

[a] Reaction conditions: alkene (1.0 mmol), $TsNH_2$ (0.82 mmol), catalyst, solvent (1.0 mL), 105 °C, time.
[b] Reaction conditions: alkene (6.0 mmol), $TsNH_2$ (3.0 mmol), catalyst, temp, time.
[c] Yields refer to isolated compounds.
[d] GaI_3 generated in situ from Ga (0.15 mmol, 5 mol%) and I_2 (0.23 mmol, 7.5 mol%).
[e] GaI_3 generated in situ from Ga (0.03 mmol, 1 mol%) and I_2 (0.05 mmol, 1.5 mol%).

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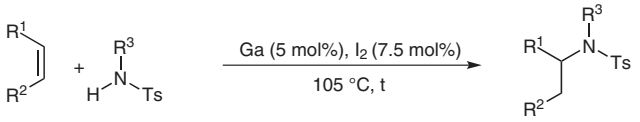
tions in the presence of either $GaBr_3$ or GaI_3 which was conveniently generated in situ from metallic gallium and iodine[6] revealed that the former catalyst does not offer any advantages over $GaCl_3$ while the latter one gives an improved yield of 96% (Table 1, entry 10). Unfortunately, worse results were obtained with in situ generated GaI_3 after a shorter reaction time (1 h), with a decreased catalyst loading (1 mol%) or at a lower temperature (90 °C, Table 1, entries 11–13). For that reason, we used the conditions of Table 1, entry 10 for all further reactions of *p*-$TsNH_2$.[8] In each case, the GaI_3 catalyst was generated in situ from 5 mol% Ga and 7.5 mol% I_2. Final control experiments performed with 5 mol% of Ga or 7.5 mol% of I_2[9] led to the conclusion that these chemicals do not show any catalytic activity when used alone.

Table 2 Intermolecular Addition of Sulfonamides to Alkenes Catalyzed by in situ Generated GaI_3[8]



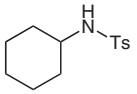
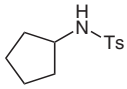
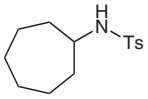
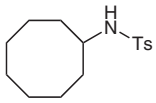
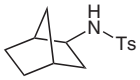
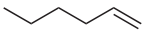
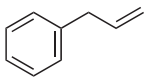
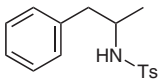
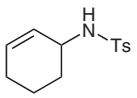
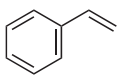
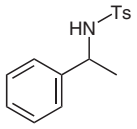
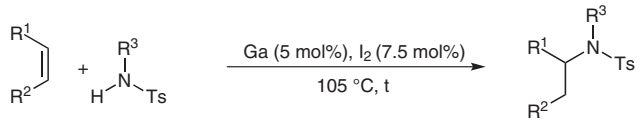
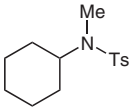
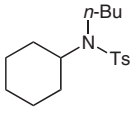
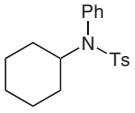
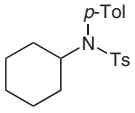
Entry	Alkene	Time (h)	R^3	Product	Yield (%)[a]
1	 **1**	2	H	 **2**	96
2	 **3**	2	H	 **11**	88
3	 **4**	2	H	 **12**	87
4	 **5**	2	H	 **13**	<5
5	 **6**	2	H	 **14**	96[b]
6	 **7**	2	H	 **15a** **15b**	81 (**15a**/**15b** = 59:41)
7	 **8**	2	H	 **16**	32
8	 **9**	2	H	 **17**	20
9	 **10**	2	H	 **18**	80[c]

Table 2 Intermolecular Addition of Sulfonamides to Alkenes Catalyzed by in situ Generated GaI_3[8] (continued)



Entry	Alkene	Time (h)	R^3	Product	Yield (%)[a]
10	 **1**	24	Me	 **19**	87
11	 **1**	24	*n*-Bu	 **20**	30
12	 **1**	24	Ph	 **21**	34
13	 **1**	24	*p*-Tol	 **22**	27

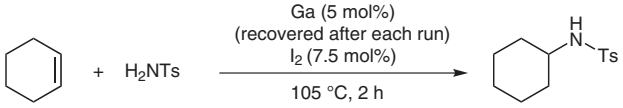
[a] Reaction conditions: alkene (6.0 mmol), sulfonamide (3.0 mmol), Ga (0.15 mmol, 5 mol%), I_2 (0.23 mmol, 7.5 mol%), 105 °C, time. Yields refer to isolated compounds.
[b] Reaction conditions: norbornene (**6**, 6.0 mmol), *p*-toluenesulfonamide (3.0 mmol), Ga (0.15 mmol, 5 mol%), I_2 (0.23 mmol, 7.5 mol%), Et_2O (1 mL), 105 °C, 2 h.
[c] Reaction conditions: styrene (**10**, 3.0 mmol), *p*-toluenesulfonamide (9.0 mmol), Ga (0.15 mmol, 5 mol%), I_2 (0.23 mmol, 7.5 mol%), THF (3 mL), 105 °C, 2 h.

In alkene scope investigations (Table 2) we found that *p*-$TsNH_2$ also reacts with cyclopentene (**3**) and cycloheptene (**4**) to give the corresponding products **11** and **12** in 88% and 87% yield, respectively. However, the corresponding reaction of cyclooctene (**5**) did not yield the expected product **13** in detectable quantities. Obviously, decomposition of cyclooctene occurred under the reaction conditions. In contrast, norbornene (**6**) underwent a smooth addition reaction with *p*-$TsNH_2$ that gave the *exo*-product **14**[7a] in 96% yield. However, in this context it must be noted that due to the low solubility of iodine in norbornene an additional low boiling solvent (diethyl ether) was added to the reaction mixture. This change in the experimental protocol was necessary in order to remove sublimated iodine from the upper parts of the Schlenk tube glass walls during the reaction. Interestingly, the reaction of 1-hexene (**7**) gave an inseparable mixture of two regioisomers which were identified to be the expected Markovnikov product **15a** and the unexpected product **15b** in a ratio of 59:41 (GC-MS, Table 2, entry 6). In the latter product the N atom of the sulfonamide is bound to the C-3 atom of the *n*-hexane chain. This observation indicates that obviously a hydrogen shift takes place under the reaction conditions prior to the nucleophilic attack of *p*-$TsNH_2$. Surprisingly, a corresponding behavior was not observed with easily isomerized allylbenzene. In this case, the Markovnikov addition product **16** was isolated as the single product, albeit with a low yield of only 32%. While a comparably poor yield (20%) was obtained with cyclohexadiene (**9**) a good result was observed with styrene which gave the desired addition product **18** in 80% yield. However, it must be noted that in this case it was necessary to use an excess of *p*-$TsNH_2$ and to add a solvent (THF) to the reaction mixture in order to minimize the amount of polymer side products. Additional reactions of cyclohexene with less reactive secondary sulfonamides (Table 2, entries 10–13) revealed that the size of the *N*-alkyl or *N*-aryl substituent of the sulfonamide seems to strongly influence the efficiency of the process. As the result, only the *N*-methyl-substituted product **19** could be obtained in good yield (87%) after a reaction time of 24 hours and strongly decreased yields were obtained for the corresponding products **20**–**22** which have *n*-Bu , Ph, or *p*-Tol substituents bound to the nitrogen atom.

During the studies mentioned so far we recognized that during reactions performed with in situ generated GaI_3 liquid gallium precipitates. In order to recycle the gallium we diluted a crude reaction mixture obtained from a corresponding standard reaction of cyclohexene (**1**) and *p*-

$TsNH_2$ with CH_2Cl_2 and removed the organic layer by syringe. From the resulting brown solution, the product **2** could be isolated in 96% yield by flash chromatography. On the other hand, we subsequently used the gallium that remained in the flask for an additional reaction of **1** with *p*-$TsNH_2$ (Table 3). For that reason, we simply added 7.5 mol% iodine and the substrates, and heated the reaction mixture to 105 °C for 2 hours. Interestingly, the product **2** could be isolated after an analogous workup procedure in unchanged yield of 96%. While a third run still gave **2** in 93% yield, the fourth run which was performed after a break of 3 weeks gave a slightly decreased yield of 81%. However, even the fifth run still gave **2** in 75% yield. The fact that during the entire sequence of 5 runs it was not necessary to add additional gallium to the reaction mixtures strongly indicates that the major amount of gallium remains in the flask after the simple removal of the organic reaction mixture. In addition, even after a number of runs, the remaining gallium is still a convenient catalyst precursor for the next in situ formation of GaI_3. For that purpose, only an additional amount of 7.5 mol% of iodine needs to be added. At the moment, we do not have a plausible mechanistic explanation for the observation that the metallic gallium precipitates again during the reactions. However, GC-MS analysis of crude reaction mixtures obtained from reactions that were performed with cyclohexene (**1**) always proved that iodocyclohexane is formed as a side product in significant quantities. This formation of an alkyl iodide can at least explain the consumption of the iodine during the course of the reaction.

Table 3 Addition of *p*-Toluenesulfonamide to Cyclohexene (**1**) Performed with Recycled Gallium



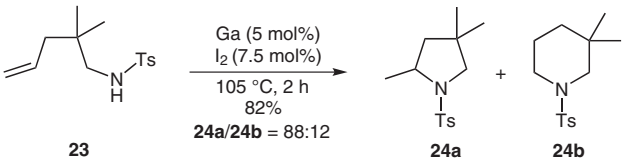
1 **2**

Entry	Run[a]	Yield **2** (%)[b]
1	1	96[c]
2	2	96
3	3	93
4	4	81[d]
5	5	75

[a] Reaction conditions: alkene (6.0 mmol), $TsNH_2$ (3.0 mmol), Ga (0.15 mmol, 5 mol%, recovered after each run), I_2 (0.23 mmol, 7.5 mol%), 105 °C, 2 h.
[b] Yields refer to isolated compounds.
[c] Run 1 was performed with fresh Ga.
[d] Run 4 was performed after a break of 3 weeks between runs 3 and 4.

Finally, we turned our attention towards the intramolecular hydroamination of tosylated amino alkene **23** (Scheme 1). Although the expected 5-*exo*-trig cyclization which leads to the formation of the cyclic sulfonamide **24a** is the major pathway of the reaction, the piperidine derivative **24b** was always formed as a side product. As described before, the reaction can be performed in various solvents (THF, Et_2O, CH_2Cl_2) but again best results were obtained under neat conditions. Under these standard conditions the products **24a** and **24b** were obtained as an inseparable mixture with a combined yield of 82% and a ratio of 88:12 (GC-MS).

In summary, we have shown for the first time that gallium(III) halides are competent catalysts for the inter- and intramolecular addition of *p*-toluenesulfonamides to alkenes. Among the halides investigated, GaI_3 which can be conveniently formed in situ from metallic gallium, and iodine was identified to be the preferred catalyst. This is particularly true because the metallic gallium can easily be recycled after each reaction. For that purpose, it is only necessary to remove the resulting crude organic reaction mixture from the metallic gallium which usually precipitates during the course of the reaction.



23 **24a** **24b**

Scheme 1 Gallium-catalyzed cyclization of a *p*-toluenesulfonylamidoalkene

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(8) **General Procedure Exemplified by the Reaction of Cyclohexene (1) with *p*-Toluenesulfonamide**
An oven-dried Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with gallium (99.9999% from Acros Organics, 11 mg, 0.15 mmol, 5 mol%) and *p*-toluenesulfonamide (514 mg, 3.0 mmol). Then the tube was evacuated and flushed with argon, and cyclohexene (**1**, 493 mg, 6.0 mmol) and iodine (58 mg, 0.23 mmol, 7.5 mol%) were added. The tube was sealed, and the resulting mixture was heated to 105 °C for 2 h. After the tube had been cooled to r.t., the reaction mixture was diluted with CH_2Cl_2 (20 mL). The resulting solution was separated from the precipitated gallium by syringe and concentrated under vacuum. Finally, the crude product was purified by flash chromatography (light PE–EtOAc, 4:1) to give sulfonamide **2** (730 mg, 2.9 mmol, 96%) as a colorless solid; mp 82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97–1.21 (m, 5 H), 1.38–1.47 (m, 1 H), 1.50–1.59 (m, 2 H), 1.63–1.70 (m, 2 H), 2.35 (s, 3 H), 2.98–3.10 (m, 1 H), 4.67 (d, $J_{H,H}$ = 7.4 Hz, 1 H, NH), 7.22 (d, $J_{H,H}$ = 8.0 Hz, 2 H), 7.70 (d, $J_{H,H}$ = 8.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, DEPT, $CDCl_3$): δ = 21.5 (CH_3), 24.6 (CH_2), 25.1 (CH_2), 33.8 (CH_2), 52.5 (CH), 126.9 (CH), 129.6 (CH), 138.4 (C), 143.0 (C) ppm. IR (neat): 1/λ = 3305, 2931, 2851, 1323, 1156, 662 cm^{-1}. HRMS (70 eV): *m/z* calcd. ($C_{13}H_{19}NO_2S$) 253.1136; found 253.1140. For the next catalytic reaction, the Schlenk tube which still contained the gallium was evacuated, flushed with argon, and charged with *p*-toluenesulfonamide (514 mg, 3.0 mmol), cyclohexene (**1**, 493 mg, 6.0 mmol) and iodine (58 mg, 0.23 mmol, 7.5 mol%), and the reaction was run as described above.

(9) The I_2-catalyzed intermolecular addition of sulfonamides to vinyl arenes has been described: Yadav, J. S.; Reddy, B. V. S.; Rao, T. S.; Krishna, B. M. *Tetrahedron Lett.* **2009**, *50*, 5351.