

# Regioselective indium(III) trifluoromethanesulfonate-catalyzed hydrothiolation of non-activated olefins

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Indium(III) trifluoromethanesulfonate was found to be an excellent catalyst for the highly regioselective intra- and intermolecular addition of thiols to non-activated olefins and could be recycled and reused without loss of activity.

The addition of thiols to non-activated olefins is a well known process for the synthesis of sulfides and generally involves a radical-type addition reaction. The radical pathway uses initiators such as peroxides, AIBN or photochemistry, and affords anti-Markovnikov-type adducts.<sup>1</sup> Some electrophilic additions affording Markovnikov-type adducts have also been reported, using strong protic acids such as perchloric, sulfuric, and *p*-toluenesulfonic acid as well as montmorillonite K10 clay.<sup>2</sup> Lewis acids such as titanium(IV), tin(IV) or aluminium(III) chlorides have been employed in over-stoichiometric amounts to promote this addition in moderate yields.<sup>3</sup> To our knowledge, no addition of thiols to non-activated olefins using catalytic amounts of a Lewis acid has yet been reported.

We present here our results on the use of indium(III) trifluoromethanesulfonate for the highly regiocontrolled and catalytic intra- and intermolecular addition of thiols to isolated olefins (Scheme 1).

Indium(III) trifluoromethanesulfonate has recently been described as an efficient catalyst in coupling reactions such as Diels–Alder and hetero Diels–Alder cycloadditions,<sup>4,5</sup> in Friedel–Craft acylations,<sup>6</sup> and in the conversion of carbonyl compounds into thioacetals or 1,3-oxathiolanes.<sup>7</sup> However, In(OTf)<sub>3</sub> has not been reported for additions to non-activated double bonds.

The cycloisomerisation of unsaturated  $\gamma,\delta$ -thiols should allow the formation of thiolane and/or thiane derivatives. For the cyclisation of model compound 4-decene-1-thiol, **1a**, several metallic triflates were tested and the most efficient catalyst was found to be aluminium and indium triflates. The expected 5- and 6-membered ring thioethers **2a** and **3a**, issued from the

intramolecular RSH addition on the two positions of the double bond, were obtained (Scheme 2).

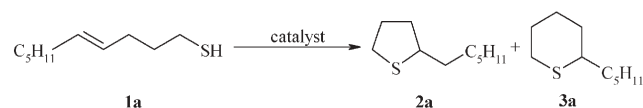
As shown in Table 1, Al(OTf)<sub>3</sub> (5 mol%) led selectively to thiolane **2a** with a **2a** : **3a** regioselectivity of 91 : 9 and an overall yield of 78% after 4 hours. In(OTf)<sub>3</sub> revealed better activity, with complete conversion after 1 hour and a cyclisation yield of 88%. A better **2a** : **3a** selectivity of 95 : 5 was obtained. We also tested the use of trifluoromethanesulfonic acid under the same conditions and 80% conversion of **1a** was attained after 6 hours, with an overall cycloisomerisation yield of 71% and partial polymerisation.

The reaction carried out in the presence of a catalytic amount of AIBN (10 mol%) in refluxing toluene led to thiane **3a** as the major product, though with very low selectivity.

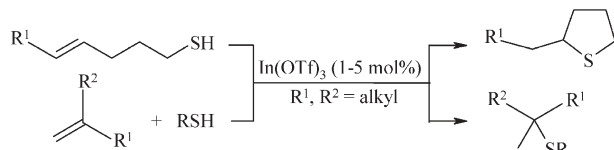
The In(OTf)<sub>3</sub>-catalyzed hydrothiolation of non-activated alkenes was then extended to the cycloisomerisation of other unsaturated thiols (Table 2, entries 1–4), using 5 mol% of catalyst. The influence of the chain length and the double bond substitution were examined by comparing the cycloisomerisation of  $\delta,\epsilon$ -unsaturated thiol **1b** and  $\gamma,\delta$ -unsaturated thiols **1a**, **1c** and **1d**.

The cycloisomerisation of 5-octene-1-thiol **1b** in refluxing nitromethane afforded thiolane **2b** and thiane **3b** in a 51 : 49 ratio and an overall yield of 58% (entry 2). The cyclisation of **1b** was expected to give thiane **3b** and the corresponding seven-membered ring thiepane. No thiepane was observed and the formation of thiolane **2b** was unexpected. The thiolane **2b** could be formed from an initial double bond isomerisation followed by cyclisation to the more stable 5-membered ring. No In(III)-catalysed double bond isomerisation process has yet been reported.

The In(OTf)<sub>3</sub>-catalyzed cycloisomerisation of  $\gamma,\delta$ -unsaturated thiols **1c** and **1d**, having a trisubstituted or 2,2-disubstituted double



Scheme 2



Scheme 1

Table 1 Cyclisation of 4-decene-1-thiol **1a** in refluxing nitromethane

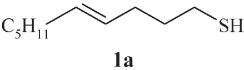
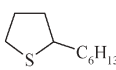
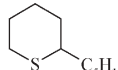
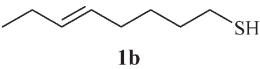
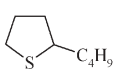
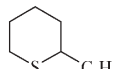
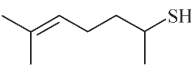
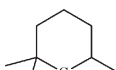
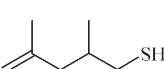
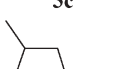
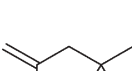
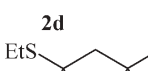
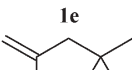
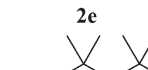
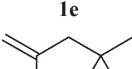
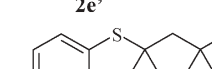
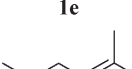
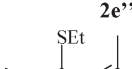
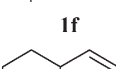
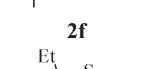

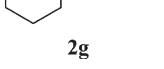
Catalyst (5 mol%)	Time/h	Conversion (%)	Yield <b>2a</b> + <b>3a</b> (%)	Selectivity <b>2a</b> : <b>3a</b> (%) <sup>a</sup>
Al(OTf) <sub>3</sub>	4	83	78	91 : 9
In(OTf) <sub>3</sub>	1	100	88	95 : 5
TfOH	6	80	71	83 : 17
AIBN <sup>b</sup>	0.5	100	88	42 : 58

<sup>a</sup> Selectivity calculated by GC. <sup>b</sup> The reaction was run in refluxing toluene with 10 mol% of the catalyst.

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**Table 2** Intra- and intermolecular In(OTf)<sub>3</sub>-catalyzed (5 mol%) hydrothiolation of olefins<sup>8</sup>

Entry	Substrates	Products	Time/h	Isolated yield <b>2</b> + <b>3</b> (%)	Regioselectivity <b>2</b> : <b>3</b> <sup>d</sup>
1 <sup>a</sup>	 <b>1a</b>	 +  <b>2a</b> <b>3a</b>	1	88	95 : 5
2 <sup>a</sup>	 <b>1b</b>	 +  <b>2b</b> <b>3b</b>	96	58	51 : 49
3 <sup>b</sup>	 <b>1c</b>	 <b>3c</b>	16	83	— : 100
4 <sup>b</sup>	 <b>1d</b>	 <b>2d</b>	1.5	91	100 : —
5 <sup>b</sup>	 <b>1e</b>	EtSH  <b>2e</b>	3	87	100 : —
6 <sup>b</sup>	 <b>1e</b>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> SH  <b>2e'</b>	15	81	100 : —
7 <sup>b</sup>	 <b>1e</b>	 <b>2e''</b>	3	79	100 : —
8 <sup>c</sup>	 <b>1f</b>	EtSH  <b>2f</b>	22	78	100 : —
9 <sup>a</sup>	 <b>1g</b>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> SH  <b>2g</b>	22	80	100 : —
10 <sup>a</sup>	 <b>1h</b>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> SH  <b>2h</b>	20	81	—

<sup>a</sup> The reaction was run in refluxing nitromethane. <sup>b</sup> The reaction was run in refluxing dichloromethane. <sup>c</sup> The reaction was run without solvent using 1 mol% of In(OTf)<sub>3</sub>. <sup>d</sup> Compounds **2** and **3** refer to the presented structures and to the corresponding regioisomers, with RSH addition to the other position of the olefin. Selectivities calculated by GC.

bond, respectively, could be run in refluxing dichloromethane with excellent yields (entries 3 and 4). Interestingly, both substrates reacted regioselectively and a single regioisomer **3c** or **2d** was obtained in each case. The comparison between entries 3 and 4 indicated that the substitution of the double bond determined the formation of the 5- or 6-membered ring thioethers, with the addition of the thiol group at the more substituted olefinic carbon following Markovnikov's rule. The rate of formation of thiolane **2d** was higher than that of thiane **3c**, probably due to the ease of formation of 5-membered rings. The cyclisation of substrates **1c** and **1d** could also be carried out with TfOH or Al(OTf)<sub>3</sub>, affording regioselectively thiane **3c** and thiolane **2d**, respectively, but with lower yields.

The In(OTf)<sub>3</sub>-catalyzed addition of thiols to differently substituted olefins was further extended to intermolecular reactions (Table 2, entries 5–10). 2,4,4-Trimethyl-1-pentene **1e** could be regioselectively functionalised both with aliphatic and aromatic thiols (entries 5–7) in refluxing dichloromethane. The thiol addition on the double bond occurred exclusively with a Markovnikov-type regioselectivity.

In the regioselective reaction of **1e** with toluenethiol (entry 7), the In(III) catalyst was recovered after evaporation of the aqueous phase and reused twice without loss of efficiency. The recycling of In(OTf)<sub>3</sub> has already been reported in other catalytic processes.

The functionalisation of a conjugated 1,3-diene substrate such as 2,5-dimethyl-2,4-hexadiene **1f** was also examined (entry 8). Diene

**1f** was converted into the corresponding sulfide **2f** with ethyl thiol using 1 mol% of In(OTf)<sub>3</sub>. The reaction could also be run without solvent and was completely regioselective, affording the thiol addition exclusively on the internal position of the diene. Interestingly, only a single thiol addition to the diene was observed even when using 2 equivalents of thiol. When diene **1f** was subject to thiol addition with AIBN (10 mol%), the reverse regioselectivity was obtained, with a ratio **2f** : **3f** of 2 : 98.

For less activated terminal and 1,2-disubstituted olefins (entries 9–10), the reactions were run in refluxing nitromethane, as with **1a**. When vinylcyclohexane **1g** was reacted with octanethiol, the expected 2-(2-cyclohexylethyl)octyl sulfide was not formed. Indeed, isomerisation of the double bond occurred (as with substrate **1b**) with the clean and selective formation of sulfide **2g** in 80% isolated yield as the single product.

*cis*-Cyclooctene **1h** was functionalised with octyl mercaptan (entry 10) to afford **2h** in 81% isolated yield.

From the point of view of the mechanism, no reaction occurred without catalyst and the classical radical-type reaction occurred at a very slow rate with light, without much selectivity and affording the opposite regioisomer. The regiochemical outcome of the In(III)-catalysed thiol addition to olefins corresponds to an acid-catalysed process. However, the In(OTf)<sub>3</sub> catalysis allows for better yields and selectivities than the corresponding TfOH catalysis, in which the olefinic substrates are subject to polymerisation. The In(III)-catalysed (5 mol%) thiol addition to **1e** (entry 5) was carried out in the presence of 2,6-di-*tert*-butylpyridine (5 mol%) as a hindered base and the thiol addition was inhibited. These data account for the important role of the protons in the catalytic process. We propose the formation of an In(III) thiolate liberating *in situ* a strong protic acid, such as TfOH or [In(RS)(OTf)<sub>2</sub>]<sup>+</sup> H<sup>+</sup>, as a key feature of the protic catalysis. The intermediate In(III) thiolate should also induce a higher nucleophilicity to the thiol moiety.

In conclusion, In(OTf)<sub>3</sub> constitutes a good and efficient catalyst both for the intra- and intermolecular addition of thiols to

non-activated olefins. The reaction is highly regioselective and occurs in a Markovnikov fashion. It can be carried out without solvent in the presence of 1 mol% of catalyst. Interestingly, the isomerisation of the C–C double bond was observed in some cases. Moreover, indium trifluoromethanesulfonate is stable in water and can be recycled and reused efficiently after evaporation of the aqueous phase.

These results report a novel example of the concept of a Lewis acid-assisted Brønsted acid-catalysed reaction.<sup>9</sup>

## Notes and references

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- 8 In a typical procedure, a mixture of olefin (5 mmol), thiol (5 mmol) and In(OTf)<sub>3</sub> (0.25 mmol) was stirred in refluxing dichloromethane or nitromethane (5 mL) depending on the substitution of the double bond of the olefin. The progress of the reaction was monitored by GC analysis. On completion of the reaction, the mixture was quenched with distilled water and extracted with Et<sub>2</sub>O. The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> and dried with MgSO<sub>4</sub>. The solvent was evaporated and the products were analysed by <sup>1</sup>H and <sup>13</sup>C NMR and mass spectrometry. In order to recycle the catalyst, the aqueous phase was washed with distilled Et<sub>2</sub>O and evaporated under vacuum.
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