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Indium(III) catalysed regio- and stereoselective hydrothiolation of bromoalkynes

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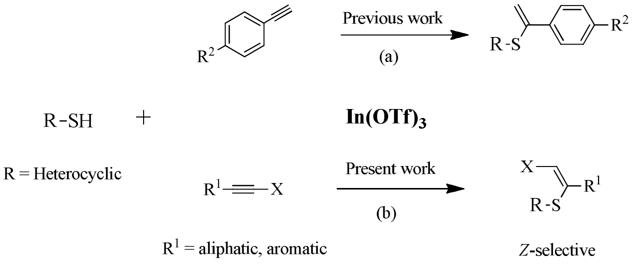
The first example of metal catalysed hydrothiolation of bromoalkynes has been demonstrated. Indium(III) trifluoromethanesulfonate was reported as the first catalyst which can catalyse the addition of thiols to bromoalkynes with absolute selectivity to generate (*Z*)-β-bromo vinyl sulfides in good yields.

Introduction

Metal catalysed addition of S-H bonds across carbon-carbon triple bonds *i.e.* hydrothiolation is one of important ongoing areas of research[1] due to the enormous importance of vinyl sulfides[2] in organic and natural product synthesis and its promising applicability as alternative to the traditional free-radical[3] and nucleophilic[4] approaches. In this regard development of efficient metal catalytic systems which can promote the hydrothiolation is of significant interest. Since the pioneered work by Sonada[5a] in 1992, numerous metal catalysed hydrothiolation protocols[5] have been developed. Although over the years significant enhancements have been made in this area, control over the selectivity is always a primary challenging parameter. Moreover considerable efforts have been made in this addition reaction with the involvement of various terminal/internal alkynes and thiols,[3-5] but the participation of haloalkynes in hydrothiolation reaction under metal catalysed conditions is still an unexplored area of research.

Haloalkynes are an important class of electron-defiecient carbon-carbon triple bonded compounds which serves as versatile synthetic valuable materials[6] in organic chemistry. In recent years functionalization of haloalkynes has been turned out to be a more promising area of research because of their versatile dual nature. In particular, transition metal catalysed coupling reactions,[7] cycloaddition reactions[8] and nucleophilic addition reactions[9] are of common interest. Although nucleophilic substitution reactions between thiols and haloalkynes are well known[10], addition reaction remains as a task which has to be explored fully. In 2011 Jianmin Dou and co-workers has reported a TBAB mediated reactions of 1, 1-dibromoalkenes with thiols[11]. In this report *in-situ* formation of bromoalkyne was achieved via TBAB promoted dehydrohalogenation of dibromoalkenes, which further undergoes base catalysed hydrothiolation. Though this method effectively access the hydrothiolation step, suffers few limitations like long reaction time, requirement of excess TBAB (5 equiv) and only aliphatic bromoalkynes undergo hydrothiolation, where as aromatic bromoalkynes undergoes cross coupling with thiols to form alkynyl sulfides. Very recently Gangguo Zhu and co-workers has reported a base promoted addition of thiols to haloalkynes[12] successfully in regio- and stereoselective manner but in all cases absolute selectivity was not achieved. Hence under such circumstances development of efficient metal catalysed methods for the direct addition of thiols to haloalkynes with challenging selectivity parameter are highly desirable. In recent years exploitation of indium catalysis[13] in organic chemistry has been geared up due to its wide range of application in various organic transformations. As a part of our continued interest on indium catalysis,[14] recently we have demonstrated an indium catalysed hydrothiolation of terminal alkynes[14e] in a challenging markovnikov mode of addition (Scheme 1: path a). In extenstion to this finding we envisioned that hydrothiolation of haloalkynes can also be achieved under identical catalytic conditions. Herein we wish to report the first example of metal catalysed hydrothiolation of bromoalkynes with high degree of regio- and stereoselectivity to generate (*Z*)-β-bromo vinyl sulfides (Scheme 2: path b). Importance of β-halo vinyl sulfides is well known, as they serve as an important synthetic intermediate[15] in organic synthesis towards the synthesis of tri/poly-substituted alkenes and vinyl sulfones.

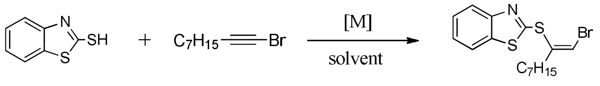


Scheme 1: Hydrothiolation of various alkynes under indium catalysed conditions.

Results and Discussion

Intially an equimolar amounts of 2-mercaptobenzthiazole (**1a**) and 1-bromonon-1-yne (**2a**) were allowed to reflux in toluene for 2h by employing 5 mol% of indium triflate as a catalyst. Formation of *Z*-selective hydrothiolated product i.e (*Z*)-2-((1-bromonon-1-en-2-yl)thio)benzo[*d*]thiazole (**3a**) in 81% yield is observed. Encouraging results like short reaction time, high degree of selectivity and metal catalysed hydrothiolation of haloalkynes for the first time motivated us to study the reaction in detail. Meanwhile when iodoalkyne was employed instead of bromoalkyne, *Z*-selective hydrothiolation took place but moderate conversion with 49% yield is observed (See Table1: entry 7). Hence in order to optimise the reaction condition, we began our studies by choosing 2-mercaptobenzthiazole (**1a**) and 1-bromonon-1-yne (**2a**) as the model substrates.

Table1: Optimization of reaction conditions[a].



1a **2a** **3a**

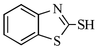
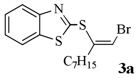
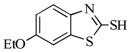
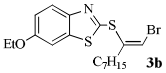
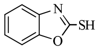
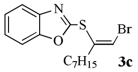
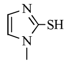
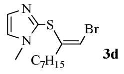
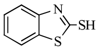
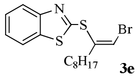
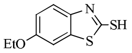
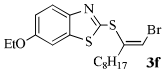
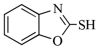
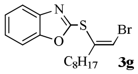
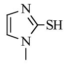
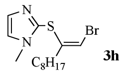
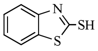
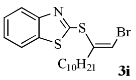
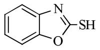
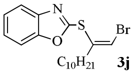
S.No	Catalyst	Solvent	Time (in h)	[b]Yield%
1	No catalyst	Toluene	5h	trace
2	$In(OTf)_3$	Toluene	2h	81
3	$In(OTf)_3$	1,2-DCE	5h	51
4	$In(OTf)_3$	Acetonitrile	5h	16
5	$In(OTf)_3$	DMF	5h	12
6	$In(OTf)_3$	DMSO	5h	10
7[c]	$In(OTf)_3$	Toluene	2h	49
8	$InCl_3$	Toluene	3h	64
9	$Sc(OTf)_3$	Toluene	5h	31
10	$Yb(OTf)_3$	Toluene	5h	39
11	$Zn(OTf)_2$	Toluene	3h	72
12	AgOTf	Toluene	3h	58
13	$Cu(OTf)_2$	Toluene	3h	41

[a]Reaction conditions: Thiol (1 mmol), bromoalkyne (1 mmol), catalyst (5 mol%), and solvent (5ml) were refuxed for specified time. [b]Isolated yield. [c]Carried out the reaction with iodoalkyne instead of bromoalkyne.

In optimization studies, indium catalysed hydrothiolation reaction under various solvents like acetonitrile, 1,2-DCE, DMF and DMSO were tried. Out of these 1,2-DCE was found out to be best as it returns the Z-isomer with 51% yield in 5h (Table1: entry 3). In case of DMF, DMSO and acetonitrile poor conversion was observed with 10-16% yield in 5h (Table1: entries 4-6). Therefore toluene was chosen as appropriate solvent for the current reaction. In next turn, we carried out the model reaction with various metal catalysts like $Sc(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$, AgOTf, $Cu(OTf)_2$ and $InCl_3$. It was observed that all the metal catalysts can access the target product (**3a**) with absolute selectivity in good to low yields. Among these $Zn(OTf)_2$ is found to be superior with 72% yield. Hence carrying out the present study by employing $In(OTf)_3$ as a catalyst in refluxing toluene is the optimised reaction condition.

With optimization reaction conditions in hand, we next began to investigate the substrate scope of the reaction. Bromoalkynes were prepared quantitatively according to the reported method[16] in literature. In the first step, we examined the reactivity of aliphatic bromoalkynes under current indium catalysed reaction conditions and the results are summarised in Table 2. Intially a series of reactions were carried out between 1-bromonon-1-yne (**2a**) and various heterocyclic thiols like 2-mercaptobenzthiazole (**1a**), 6-ethoxy-2-mercaptobenzthiazole (**1b**), 2-mercapto benoxazole (**1c**) and 1-methylimidazole-2-thiol (**1d**) respectively in the presence of 5 mol% indium triflate. In all cases hydrothiolation took place exclusively with absolute selectivity and good to moderate yields were observed within a time span of 2-5h (See table 2: entries 1-4). Similarly other aliphatic bromoalkynes like 1-bromodec-1-yne (**2b**) and 1-bromododec-1-yne (**2c**) were also tested. (**2b)** undergoes the addition reaction with (**1a**), (**1b**), and (**1c**) in expected selective manner with 76%, 61% and 71% yields respectively (See table 2: entries 5-7) but moderate conversion was observed with (**1d**) (See table 2: entry 8). Good yields were observed when 1-bromo-dodec-1-yne (**2c**) was treated with 2-mercaptobenzthiazole (**1a**) and 2-mercapto benzoxazole (**1b**) within a short time of 2-3h (See table 2: entries 9-10). As mentioned earlier in all cases hydrothiolation took place exclusively and no side products were observed.

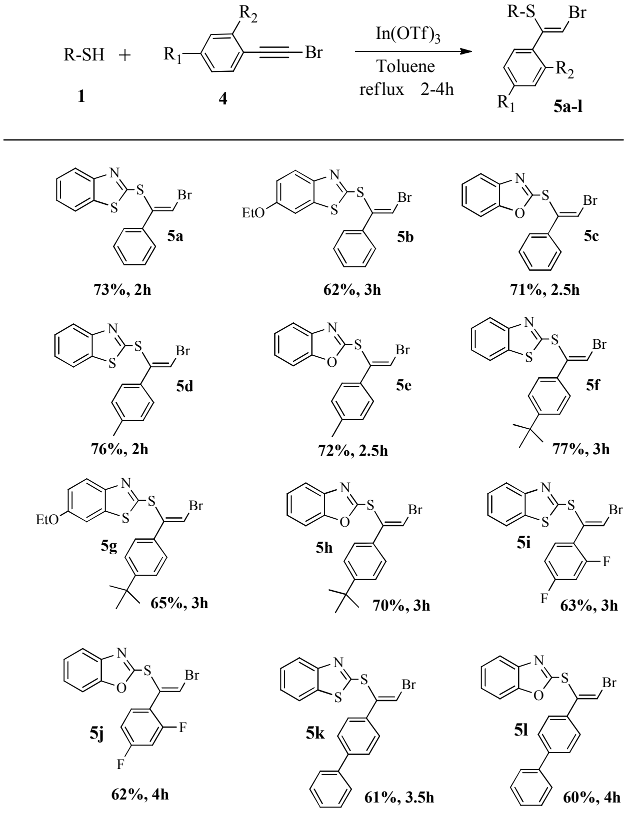
Table 2: Hydrothiolation of aliphatic bromoalkynes[a]

Entry	Thiol	Bromoalkyne	Product	Time	[b]Yield%
1		C_7H_{15}—≡—Br **2a**	 **3a**	2h	81
2		**2a**	 **3b**	2h	68
3		**2a**	 **3c**	3h	74
4		**2a**	 **3d**	5h	59
5		C_8H_{17}—≡—Br **2b**	 **3e**	2h	76
6		**2b**	 **3f**	2.5h	61
7		**2b**	 **3g**	3h	71
8		**2b**	 **3h**	6h	51
9		$C_{10}H_{21}$—≡—Br **2c**	 **3i**	2h	70
10		**2c**	 **3j**	3.5h	66

[a]Reaction conditions: Thiol (1 mmol), bromoalkyne (1 mmol), catalyst (5 mol%) and toluene (5ml) were refluxed for specified time. [b]Isolated yield.

In the next attempt we turned our attention to check the reactivity of aromatic bromoalkynes under current indium catalysed conditions. In the presence of 5 mol% of indium triflate, when 2-mercaptobenzthiazole (**2a**) was treated with (bromoethynyl) benzene (**4a)** in refluxing toluene for 2h afforded the hydrothiolated product (*Z*)-2-((2-bromo-1-phenylvinyl)thio)benzo[*d*]thiazole (**5a**) in 73% yield. It was quite interesting that the hydrothiolation took place exclusively and no side products like alkynyl sulfides were detected. It is evident that aromatic bromoalkynes undergoes nucleophilic substitution[11] rather than addition under previously reported conditions. With the optimized reaction condition, various aromatic bromoalkynes and heterocyclic thiols underwent the hydrothiolation smoothly within a short time of 2-4h and the results are summarized in Table 3. Aromatic bromalkynes bearing electron-donating groups on aromatic ring undergoes the hydrothiolation with various heterocyclic thiols and afforded the target products in good yields (Table 3, entries 5d-5h). Bromoalkyne containing halogen substitutions on the aromatic ring undergoes the reaction with (**2a**), (**2b)** smoothly with 63%, 62% yield (Table 3, entries 5i-5j). It is noteworthy that under current reaction conditions, biphenyl ring containing bromoalkynes also participated in hydrothiolation reaction with (**2a**) and (**2b**) in selective manner and returns good yield in 3-4h (Table 3, entries 5k-5l).

Table 3: Hydrothiolation of aromatic bromoalkynes[a].



[a] Reaction conditions: Thiol (1mmol), aromatic bromoalkyne (1 mmol), 5 mol% In(OTf)$_3$ were refluxed in toluene (5ml) till reaction is complete. [b] Yield of isolated product

Although the mechanistic studies were not carried out, we proposed that the reaction might proceeds through the formation of indium sulfide complex in the first step followed by the regioselective trans addition of thiol to bromoalkynes to generate the corresponding (*Z*)-β-bromo vinyl sulfides[5j]. It was important to mention that under present reaction conditions bromoalkynes undergo hydrothiolation with heterocyclic thiols successfully but effects to activate aromatic and aliphatic thiol were failed. Formation of disulfides *via* homocoupling of thiols was observed. This can be explained on the basis of our previous report[14e], in which heterocyclic thiols undergoes markovnikov addition via formation of indium sulfide complex whereas aromatic/aliphatic thiols undergoes anti-markovnikov addition *via* indium alkynylide from indium triflate and terminal alkyne. We predicted that the difference in nucleophilic character of thiols is responsible for this selectivity switch. Hence the formation of indium alkynylide complex was completely ruled out with haloalkynes, aromatic/aliphatic thiols were not participated under present reaction conditions. Further studies are underway to explore the catalytic system which can activate the thiols other than heterocyclic thiols in hydrothiolation reaction

Conclusions

In conclusion we have demonstrated the hydrothiolation of haloalkynes for the first time under metal catalysed conditions with absolute regio- and stereoselectivity. In(OTf)$_3$ has shown the remarkable ability to catalyse the addition of thiols to bromoalkynes successfully and fullfill the primary challenge i.e. selectivity control in hydrothiolation reaction. Attractive features like short reaction time, good yield, high degree of selectivity, variety in substrate scope, no requirement of inert atmosphere and additional additives and absence of any side products makes it a useful protocol.

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Notes and references

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1. For recent review see: R. Castarlenas, A. D. Giuseppe, J. J. Perez-Torrente and L. A. Oro, *Angew. Chem. Int. Ed.,* **2013**, 15, 211-222.
2. (a) M. Bratz, W. H. Bullock, L. E. Overman and T. Takemoto, *J. Am. Chem. Soc.,* **1995**, 117, 5958–5966. (b) H. Mizuno, K. Domon, K. Masuya, K. Tanino and I. Kuwajima, *J. Org. Chem.,* **1999**, 64, 2648–2656. (c) W. H. Pearson, I. Y. Lee, Y. Mi and P. J. Stoy, *J. Org. Chem.,* **2004**, 69, 9109–9122. (a) T. Mukaiyama, K. Kamio, S. Kobayashi and H. Takei, *Bull. Chem. Soc., Jpn.* **1972**, 4, 193–202. (b) E. Wenkert, T. W. Ferreira and E. L. Michelotti, *J. Chem. Soc., Chem. Commun.,* **1979**, 6, 637–638. (c) B. M. Trost and A. C. Lavoie, *J. Am. Chem. Soc.,* **1983**, 105, 5075–5090. (d) A. Sabarre and J. A. Love, *Org. Lett.*, **2008**, 10, 3941–3944.
3. (a) M. E. Peach, *The Chemistry of the Thiol Group*, Patai, S., Ed., Vol. 2, **1974**, Wiley, London. b) L. Benati, L. Capella, P. C. Montevecchi, P. Spagnolo, *J. Chem. Soc., Perkin Trans. 1* **1995**, 1035-1038. (c) K. Griesbaum, *Angew. Chem. Int. Ed.,* **1970**, 9, 273–287. (d) Y. Ichinose, K. Wakamatsu, K. Nozaki, J.-L. Birbaum, K. Oshima and K. Utimoto, *Chem. Lett.,* **1987**, 16, 1647–1650. (e) M. L. Conte, S. Pacifico, A. Chambery, A. Marra, A. Dondoni, *J. Org. Chem.,* **2010**, 75, 4644-4647.
4. (a) W. E. Truce, H. E. Hill, M. M. Boudakian, *J. Am. Chem. Soc.,* **1956**, 78, 2756-2762. (b) V. X. Truong and A. P. Dove, *Angew. Chem. Int. Ed.,* **2013**, 4132-4136.
5. (a) H. Kuniyasu, A. Ogawa, K-I. Sato, I. Ryu, N. Kambe, N. Sonoda, *J. Am. Chem. Soc.,* **1992**, 114, 5902-5903. (b) C. Cao, L. R. Fraser, and J. A. Love, *J. Am. Chem. Soc.,* **2005**, 127, 17614–17615. (c) J. Yang, A. Sabarre, L. R. Fraser, B. O. Patrick and J. A. Love, *J. Org. Chem.,* **2009**, 74, 182–187. (d) L. R. Fraser, J. Bird, Q. Wu, C. Cao, B. O. Patrick and J. A. Love, *Organometallics*, **2007**, 26, 5602–5611. (e) C. J. Weiss, S. D. Wobser and T. J. Marks, *J. Am. Chem. Soc.,* **2009**, 131, 2062–2063. (f) C. J. Weiss and T. J. Marks, *J. Am. Chem. Soc.,* **2010**, 132, 10533–10546. (g) (b) V. P. Ananikov, D. A. Malyshev, I. P. Beletskaya, G. G. Aleksandrov and I. L. Eremenko, *Adv. Synth. Catal.,* **2005**, 347, 1993–2001. (h) D. A. Malyshev, N. M. Scott, N. Marion, E. D. Stevens, V. P. Ananikov, I. P. Beletskaya and S. P. Nolan, *Organometallics*, **2006**, 25, 4462–4470. (i) S. Kanakala, S. Nerella, R. Vadde, C. S. Vasam, *RSC. Adv.*, **2013**, 3, 23582-23588. (j) A. Ogawa, T.

Ikeda, K. Kimura, T. Hirao, *J. Am. Chem. Soc.,* **1999**, 121, 5108-5114.

6. (a) A. Trofimov, N. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.,* **2008**, 130, 13538-13539. (b) S. Nicolai and J. Waser, *Org. Let.,* **2011**, 13, 6324-6327. (c) Y. Li, X. Liu, H. Jiang, Z. Feng, *Angew. Chem. Int. Ed.,* **2010**, 49, 3338-3341. (d) Y. Liu, B. Shen, M. Kotora, T. Takahashi, *Angew. Chem. Int. Ed.,* **1999**, 38, 949-952. (e) B. C. Chary, S. Kim, D. Shin, P. H. Lee, *Chem. Commun.,* **2011**, 47, 7851-7853. (f) X. Chen, W. Kong, H. Cai, L. Kong, G. Zhu, *Chem. Commum.,* **2011**, 47, 2164-2166.
7. Y. Weng, B. Cheng, C. He, A. Lei, *Angew. Chem. Int. Ed.,* **2012**, 51, 9547-9551. (b) S. Hirano, R. Tanaka, H. Urabe, F, Sato, *Org. Let.,* **2004**, 6, 727-729. (c) C. Laroche, J. Li, M. W. Freyer, and S. M. Kerwin, *J. Org. Chem.,* **2008**, 73, 6462-6465. (d) Y. Li, J. Zhao, H. Chen, B. Liu, H. F. Jhang, *Chem. Commum.,* **2012**, 48, 3545-3547. (e) H. Liu, C. Chen, L. Wang, X. Tong, *Org. Let.,* **2011**, 13, 5072-5075. (f) Z. Chen, H. Jiang, A. Wang, S. Yang, *J. Org. Chem.,* **2010**, 75, 6700-6703.
8. (a) K. Villeneuve, N. Riddell, R. W. Jordan, G. C. Tsui, W. Tam, *Org. Let.,* **2004**, 6, 4543-4546. (b) Y. Yamamoto, K. Hattori, H. Nishiyama, *J. Am. Chem. Soc.,* **2006**, 128, 8336-8340. (c) A. Allen, K. Villeneuve, N. Cockburn, E. Fatila, N. Riddell, W. Tam, *Eur. J. Org. Chem.,* **2008**, 4178-4192.
9. (a) W. Zeng, W. Wu, H. Jiang, Y. Sun, Z. Chen, *Tetrahedron Lett.,* **2013**, 54, 4605-4609. (b) S. Wang, P. Li, L. Yu, L. Wang, *Org. Let.,* **2011**, 13, 5968-5971. (c) Z. Chen, J. Li, H. Jiang, S. Zhu, Y. Li, C. Qi, *Org. Let.,* **2010**, 12, 3262-3265. (d) Z. Chen, J. Li, H. Jiang, Y. Li, C. Qi, *Chem. Commum.,* **2010**, 46, 8049-8051.
10. G. R. Ziegler, C. A. Welch, C. E. Orzech, S. Kikkawa, S. I. Miller, *J. Am. Chem. Soc.,* **1963**, 85, 1648-1651.
11. H. Xu, S. Gu, W. Chen, D. Li, J. Dou, *J. Org. Chem.,* **2011**, 76, 2448-2458.
12. G. Liu, L. Kong, J. Shen, G. Zhu, *Org. Biomol. Chem.,* **2014,** 12, 2310-2321.
13. For reviews see: (a) J. S. Yadav, A. Antony, J. George, B. V. S. Reddy, *Eur. J. Org. Chem.,* **2010**, 591-605. (b) M. S. Singh and K. Raghuvanshi, *Tetrahedron*, **2012**, 8683-8697.
14. (a) H. N. Borah, D. Prajapati and R. C. Boruah, *Synlett*. **2005**, 2823–2825. (b) K. C. Lekhok, D. Prajapati, R. C. Boruah, *Synlett*. **2008**, 655–658. (c) D. Prajapati, R. Sarma, D. Bhuyan, W. Hu, *Synlett*. **2011**, 627–630. (d) R. Sarma and D. Prajapati, *Chem. Commun.,* **2011**, 47, 9525–9527. (e) R. Sarma, N. Rajesh, D. Prajapati, *Chem. Commun.,* **2012**, 48, 4014-4016. (f) M. M. Sarmah, D. Bhuyan, D. Prajapati, *Synlett*. **2013**, 24, 2245-2248.
15. H. Xu, W. Chen, J. Chen, H. Wu, *Synthesis.* **2012**, 44, 380-388. (b) A. B. V. K. Kumar, K. S. V. K Rao, M. Maheswara, M. C. S. Subba, S. Cui, D. Jin, Y-I. Lee, *Bull. Korean. Chem. Soc.,* **2008**, 29, 2291-2294.
16. M. Rosenthal, L. Li, J. J. Hernandez, X. Zhu, D. A. Ivanov, M. Moller, *Chem. Eur. J.*, **2013**, 19, 4300 – 4307.

Indium(III) catalysed regio- and stereoselective hydrothiolation of bromoalkynes

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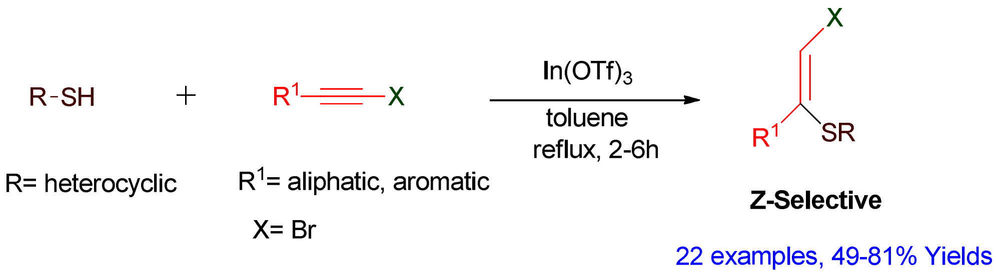

Hydrothiolation of bromoalkynes has been reported for the first time under metal catalysed conditions. Indium(III) trifluoromethanesulfonate was demonstrated as the first catalyst which can catalyse the hydrothiolation of bromoalkynes with absolute regio- and stereoselectivity to generate synthetically valuable (*Z*)-β-bromo vinyl sulfides in good yields.