Communication

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α-C–H Alkylation of Methyl Sulfides with Alkenes by a Scandium Catalyst

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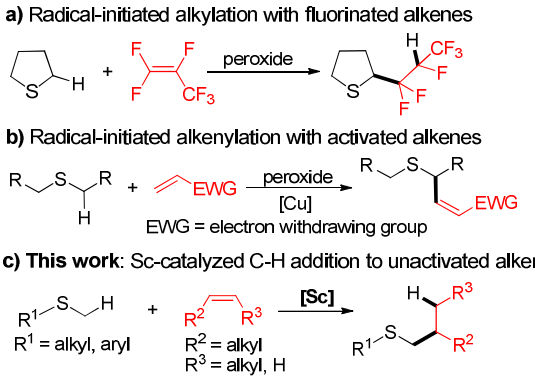
Supporting Information Placeholder

ABSTRACT: The C–H addition of sulfides to alkenes is an atom-efficient route for the functionalization and modification of sulfide compounds through C–C bond formation, but this transformation is highly challenging. We report here the regioselective α-C(sp^3)–H addition of a wide range of methyl sulfides to a variety of olefins and dienes by a half-sandwich scandium catalyst. This protocol provides a unique route for the synthesis of diverse sulfide derivatives through C–C bond formation at a sulfur-adjacent carbon atom in a 100% atom efficient fashion.

Sulfide motifs are important components in a large number of natural products, bioactive molecules, functional materials, and organocatalysts.[1] Therefore, the development of efficient and selective routes for the functionalization of sulfides is of great interest and importance. Among possible approaches, the C–H addition of a sulfide compound to alkenes is the most atom-efficient route for the synthesis of alkylated sulfide derivatives.[2] However, this transformation is highly challenging and has met with only limited success to date, partly because a sulfide unit often acts as a poison to transition metal catalysts[3] and can also easily undergo C–S bond cleavage in the presence of a transition metal catalyst.[4] There are a number of reports of the use of MeS as a directing group for transition metal-catalyzed C–H activation.[5] The α-C–H functionalization of some sulfides by cross-dehydrogenative coupling (CDC) has also been reported.[6] Regarding the C–H addition of sulfides to alkenes,[7] the reaction of tetrahydrothiophene with fluorinated alkenes in the presence of a peroxide was reported to give the corresponding α-C–H alkylation product via a radical-initiated mechanism (Scheme 1a).[7a] Under the coexistence of a copper compound and a peroxide, the reaction of sulfides with some activated alkenes yielded the alkenylated products (Scheme 1b).[7d] In all of these reactions, only alkenes having an electron-withdrawing group showed reactivity, and symmetrically substituted sulfides were usually used as a reaction partner to avoid regioselectivity problems. The regioselective catalytic α-C(sp^3)–H addition of a sulfide compound bearing two different hydrocarbon substituents to an unactivated alkene has not been reported previously (See Scheme 1c).

We have recently found that the interaction between a heteroatom (such as oxygen, nitrogen, and sulfur) and a rare earth metal can effectively enhance various rare-earth-catalyzed transformations,[8,9] such as the regioselective methylalumination of alkenes and alkynes,[9a] ortho-selective aromatic C–H addition to alkenes,[9b,c,e] and the syndiospecific polymerization of α-olefins.[9h] These findings invoked our interest in the catalytic C–H addition of sulfides to alkenes by rare earth catalysts. We report here the unprecedented hydrothiomethylation of a variety of olefins and dienes with a wide range of methyl sulfides by a half-sandwich scandium catalyst. This work represents the first example of regioselective catalytic α-C(sp^3)–H addition of sulfides to unactivated alkenes, efficiently affording diverse sulfide derivatives through C–C bond formation at a sulfur-adjacent carbon atom (Scheme 1c).

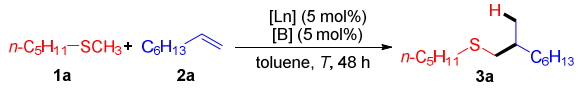
Scheme 1. α-C–H Functionalization of Sulfides with Alkenes



At first, we screened a series of rare earth catalysts bearing different ligands for the reaction of *n*-pentyl methyl sulfide (**1a**) with 1-octene (**2a**) in toluene at 70 °C (Table 1). A combination of the scandium tris(*o*-*N*,*N*-dimethylaminobenzyl) complex **Sc-1** with one equiv. of $[Ph_3C][B(C_6F_5)_4]$ yielded a trace amount of the hydrothiomethylation product **3a** in 48 h (Table 1, entry 1). The C_5H_5-ligated scandium bis(*o*-*N*,*N*-dimethylaminobenzyl) complex **Sc-2** was inactive under the same conditions (Table 1, entry 2). In contrast, the C_5Me_5-

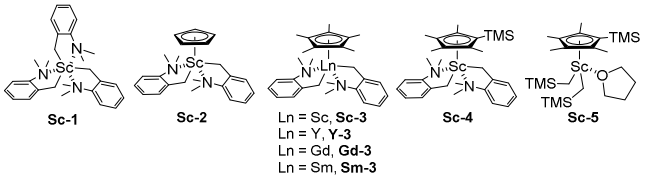
ligated analog **Sc-3** afforded the desired hydrothiomethylation product **3a** in 88% yield (Table 1, entry 3). The analogous rare earth complexes of larger metals such as **Y-3**, **Gd-3** and **Sm-3** were much less effective (Table 1, entries 4-6). These results suggest that the catalyst activity is significantly influenced by the supporting Cp ligands as well as the rare earth metals.[10] The $C_5Me_4SiMe_3$-ligated scandium complex **Sc-4** showed similar activity (86% yield, Table 1, entry 7) as that of **Sc-3**. The THF-bonded scandium trimethylsilylmethyl analog **Sc-5** gave a slightly lower yield (63% yield, Table 1, entry 8), probably due to the influence of the THF Lewis base ligand that could hamper the access of the sulfide **1a** or the alkene **2a** to the metal center.[11] Either the neutral scandium complex **Sc-3** or $[Ph_3C][B(C_6F_5)_4]$ alone showed no catalytic activity (Table 1, entry 9 and 10), suggesting that a cationic half-sandwich scandium alkyl species is essential in this reaction. When **Sc-3a**/$[Ph_3C][B(C_6F_5)_4]$ was used as a catalyst, a shorter reaction time (24 h) or lower temperature (50 °C) led to a lower yield of **3a** (81% and 69%, respectively). The reaction at 90 °C did not give a higher yield (87%).

Table 1. Catalyst screening for hydrothiomethylation of 1-octene with pentyl methyl sulfide[a]



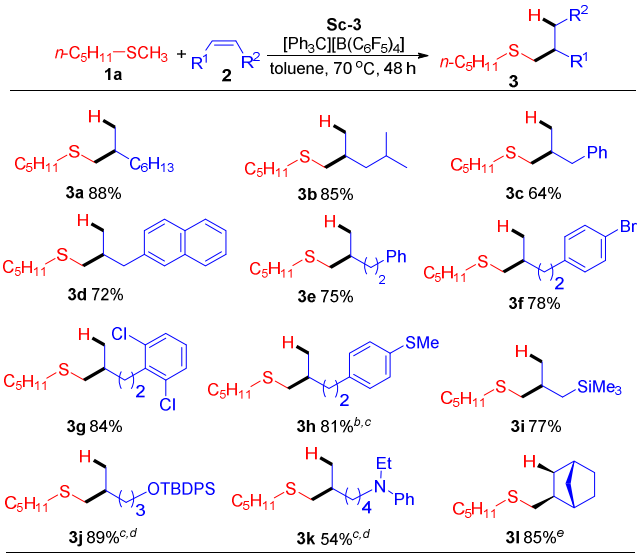
Entry	[Ln]	[B]	Yield (%)
1	**Sc-1**	$[Ph_3C][B(C_6F_5)_4]$	< 5
2	**Sc-2**	$[Ph_3C][B(C_6F_5)_4]$	< 5
3	**Sc-3**	**$[Ph_3C][B(C_6F_5)_4]$**	**88**
4	**Y-3**	$[Ph_3C][B(C_6F_5)_4]$	< 5
5	**Gd-3**	$[Ph_3C][B(C_6F_5)_4]$	10
6	**Sm-3**	$[Ph_3C][B(C_6F_5)_4]$	< 5
7	**Sc-4**	$[Ph_3C][B(C_6F_5)_4]$	86
8	**Sc-5**	$[Ph_3C][B(C_6F_5)_4]$	63
9	**Sc-3**	--	n.r.
10	--	$[Ph_3C][B(C_6F_5)_4]$	n.r.

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.6 mmol, 1.5 equiv.), $[Ph_3C][B(C_6F_5)_4]$ (5 mol%), [Ln] (5 mol%), toluene (2.0 mL), 70 °C, 48 h, isolated yield.



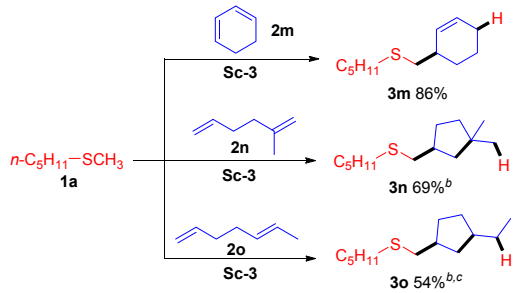
We then examined the reaction of pentyl methyl sulfide (**1a**) with various olefins (**2**) under the optimized conditions (Table 2). Olefins containing either aliphatic or aromatic substituents all reacted with **1a** in the presence of 5 mol % of **Sc-3** and $[Ph_3C][B(C_6F_5)_4]$, exclusively affording the corresponding branched hydrothiomethylation products (such as **3a-3e**) in moderate to high yields. Aromatic C–Br and C–Cl bonds were compatible with the catalyst (see **3f** and **3g**). In the case of *p*-$MeSC_6H_5CH_2CH_2CH{=}CH_2$ (**2h**), the C–H activation exclusively took place at the methyl group of **1a** to give the corresponding intermolecular hydrothiomethylation product **3h** in 81% isolated yield, while the MeS group bonded to the phenyl group in **2h** remained intact. This strongly supports a reaction mechanism involving sulfur coordination, as the coordination ability of an aryl thioether is weaker than that of an alkyl thioether. Trimethylsilyl (**3i**), siloxy (**3j**), and amino (**3k**) groups were also compatible.[12] The reaction of **1a** with norbornene gave the desired hydrothiomethylation product **3l** in 85% yield with excellent diastereoselectivity. An acyclic internal alkene such as *cis*-2-octene did not undergo the hydrothiomethylation reaction under the same conditions probably due to steric hindrance. In the case of styrene, the polymerization of styrene was observed.[13]

Table 2. Hydrothiomethylation of various olefins with pentyl methyl sulfide by Sc-3[a]



[a]Reaction conditions: **1a** (0.4 mmol), **2** (0.6 mmol, 1.5 equiv.), **Sc-3** (5 mol%), $[Ph_3C][B(C_6F_5)_4]$ (5 mol%), toluene (2.0 mL), 70 °C, 48 h, isolated yield, unless otherwise noted. [b]**1a** (0.6 mmol), **2** (0.4 mmol). [c]**Sc-3** (10 mol%), $[Ph_3C][B(C_6F_5)_4]$ (10 mol%). [d]**1a** (0.8 mmol), **2** (0.4 mmol). [e]>20:1 dr

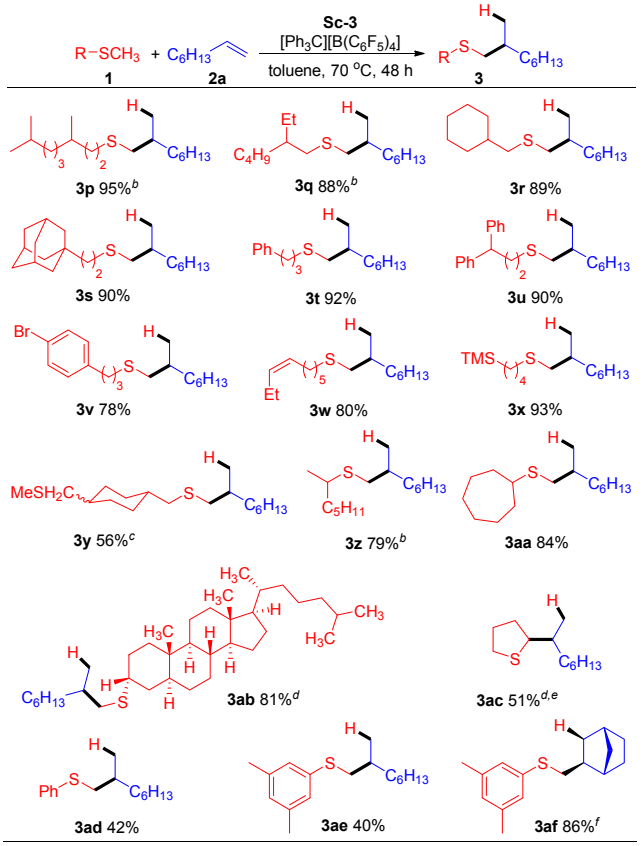
Scheme 2. Hydrothiomethylation of dienes with pentyl methyl sulfide[a]



[a]Reaction conditions: **1a** (0.4 mmol), **2** (0.6 mmol, 1.5 equiv.), **Sc-3** (5 mol%), $[Ph_3C][B(C_6F_5)_4]$ (5 mol%), toluene (2.0 mL), 70 °C, 48 h, isolated yield. [b]**Sc-3** (10 mol%), $[Ph_3C][B(C_6F_5)_4]$ (10 mol%). [c]1.7 : 1 dr.

Dienes could also be efficiently hydrothiomethylated with **1a** (Scheme 2). The reaction of 1,3-cyclohexadiene (**2m**) with **1a** in the presence of 5 mol % of **Sc-3** and $[Ph_3C][B(C_6F_5)_4]$ yielded the corresponding thiomethylated cyclohexene product **3m** through C–H addition to the 1,3-diene unit in a 1,4-fashion.[14] More remarkably, in the case of unconjugated 1,5-dienes such as **2n** and **2o**, the hydrothiomethylation was accompanied by cyclization through sequential insertion of the two C=C bonds, which afforded the corresponding thiomethyl-functionalized cyclopentane derivatives **3n** and **3o**, respectively.

Table 3. Hydrothiomethylation of 1-octene with various alkyl methyl sulfides [a]

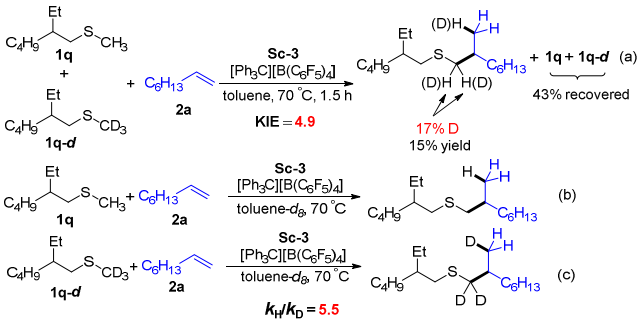


[a]Reaction conditions: **1** (0.4 mmol), **2a** (0.6 mmol), **Sc-3** (5 mol%), $[Ph_3C][B(C_6F_5)_4]$ (5 mol%), toluene (2.0 mL), 70 °C, 48 h, isolated yield, unless otherwise noted. [b]1:1 dr. [c]**1** (0.8 mmol), **2a** (0.4 mmol). [d]1.3:1 dr. [e]**Sc-3** (10 mol%), $[Ph_3C][B(C_6F_5)_4]$ (10 mol%). [f]Norbornene (0.6 mmol) was used instead of 1-octene, and >20:1 dr.

Table 3 summarizes the reactions of 1-octene (**2a**) with various alkyl (or phenyl) methyl sulfides (**1**). The alkyl methyl sulfides containing either acyclic or cyclic aliphatic groups or aromatic groups could be smoothly incorporated into the alkene substrate to give the corresponding hydrothiomethylation products (such as **3p**-**3v**) in high yields. The reaction exclusively occurred at the methyl group of the sulfides, while the methylene unit remained intact, probably due to steric influence. An internal alkene moiety (**3w**) and the $SiMe_3$ group (**3x**) in the sulfides survived the reaction conditions. The mono-alkylation of 1,4-bis(methylthiomethyl)cyclohexane that contains two SCH_3 groups could be selectively achieved (**3y**) when an excess amount of the sulfide was employed. The methyl sulfides having a sterically demanding secondary alkyl (**3z**) or cyclooctyl substituent (**3aa**) directly bonded to the sulfur atom did not hamper the reaction at the SMe group. The selective formation of **3ab** (81% yield) in the reaction of **2a** with 3-methylthiocholestane further demonstrated the useful potential of this protocol in the alkylation of a methyl sulfide having a complex substituent. The α-methylene C–H alkylation of tetrahydrothiophene with **2a** could also achieved albeit with a higher catalyst loading (10 mol %) (**3ac**). An acyclic dialkyl sulfide such as *n*-Butyl ethyl sulfide did not undergo C–H alkylation under the same conditions probably due to steric hindrance.

It is also worth noting that in the reaction of methyl phenyl sulfide with **2a**, the sp^3 methyl C–H bond, rather than the sp^2 ortho-C–H bond of the phenyl group, was selectively alkylated to give **3ad**. This is in sharp contrast with what was observed previously in the scandium-catalyzed reaction of anisole with alkenes, in which the reaction exclusively occurred at the sp^2 ortho-C–H bond of the phenyl group.[9c] Although the reactivity of methyl phenyl sulfide toward 1-octene (**2a**) was lower than that of a methyl alkyl sulfide probably because of the electron-withdrawing influence of the phenyl group, the reaction of a methyl phenyl sulfide with norbornene (which is more reactive than 1-octene) efficiently took place, affording the corresponding thiomethyl-functionalized norbornane derivative (such as **3af**) in high yield.

Scheme 3. Kinetic isotope effect experiments

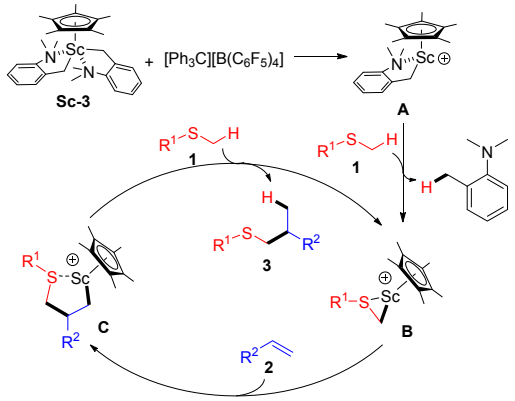


To gain information on the reaction mechanism, a 1:1 mixture of the sulfide **1q** and the methyl-deuterated sulfide **1q-*d*** was used to react with 1-octene under the standard reaction conditions (Scheme 3a). The ^1H NMR analysis of the product at the stage of 15% yield revealed a significant kinetic isotope effect (KIE = 4.9). No H/D exchange was observed between **1q** and **1q-d**. The relative ratio of the initial rates of the two side-by-side reactions using **1q** and **1q-*d***, respectively, was determined to be 5.5 (Schemes 3b and 3c). These results suggest that the C–H activation of the methyl group in the sulfides is involved in the rate-determining step.

A possible reaction mechanism is depicted in Scheme 4. Similar to the hydroaminoalkylation of alkenes with tertiary

amines reported previously,[9f] the coordination of the sulfur atom of a methyl sulfide **1** to the Sc atom in the cationic half-sandwich scandium aminobenzyl species **A**, which was generated by the reaction of **Sc-3** with $[Ph_3C][B(C_6F_5)_4]$,[15] followed by C–H activation (deprotonation) of the methyl group in **1** by the benzyl species could give a three-membered metallacycle intermediate like **B** with release of *N*,*N*-dimethyl-*o*-toluidine. This step was supported by observation of the formation of $CH_2DC_6H_4NMe_3$-*o* in the reaction of $CD_3SCH_2CH(Et)(^nC_4H_9)$ with **2a** catalyzed by **Sc-3**/$[Ph_3C][B(C_6F_5)_4]$ (see Supporting Information). The insertion of an alkene **2** into the C–Sc bond in **B** would give **C**, which on hydrogen abstraction of the methyl group in **1** should release the final product **3** and regenerate the active species **B**.

Scheme 4. Proposed reaction mechanism. The counter anion in A, B and C is omitted for clarity.



In summary, we have achieved for the first time the hydrothiomethylation of a variety of olefins and dienes with a series of methyl sulfides by using a half-sandwich scandium catalyst such as **Sc-3**. This protocol offers an atom-efficient route for the modification and functionalization of sulfides through the regiospecific α-C–H addition to a C=C double bond, leading to formation of a new family of sulfide derivatives with diversified substituents. The success of this transformation is obviously due to the unique affinity and reactivity of cationic scandium alkyl species towards a sulfide group and C–H and C=C bonds. We expect these unique features could also be applied to other related transformations. Studies along this line are currently in progress.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(10) Similar metal and ligand influences were also observed in rare-earth-catalyzed olefin polymerization (see: ref. 8). This is probably due to the stability (or lifetime) of the resulting cationic half-sandwich rare earth metal monoalkyl active species.

(11) Addition of THF to the THF-free Sc complex **Sc-4** deactivated the catalyst. The similar THF influence on olefin polymerization was also observed previously. See: Li, X.; Nishiura, M.; Hu, L.; Mori, K.; Hou, Z. *J. Am. Chem. Soc*. **2009**, *131*, 13870.

(12) The use of an excess amount of the sulfide **1a** was needed to achieve a significant yield of the desired products (**3j,k**) in the case of alkenes containing a siloxy or amino group, because the coordination of the siloxy or amino group could compete with that of the sulfide unit.
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