ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2024, **60**, 1794

Received 20th December 2023,
Accepted 16th January 2024

DOI: 10.1039/d3cc06194a

rsc.li/chemcomm

Synthesis of highly substituted 1,3-dienes through halonium promoted 1,2-sulfur migration of propargylic thioethers†

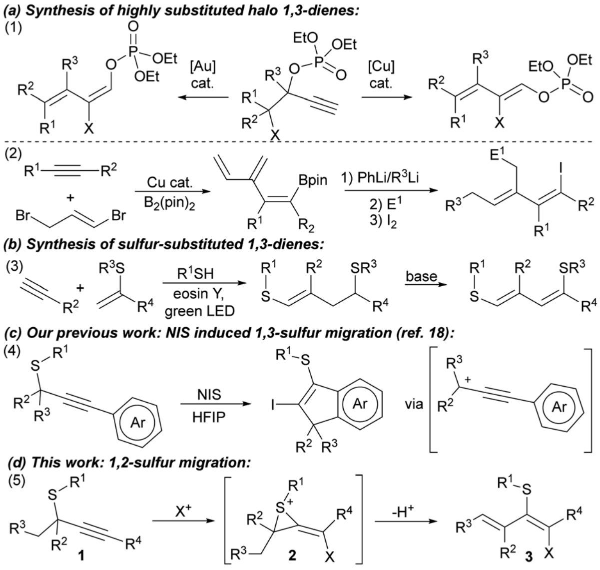
Clara Martínez-Núñez, Noelia Velasco, Roberto Sanz and Samuel Suárez-Pantiga *

Conjugated 1-bromo or 1-iodo-1,3-dienes bearing a sulfide substituent have been synthesized *via* 1,2-sulfur migration from propargylic thioethers upon activation with NIS or NBS. The reaction generally proceeds with high control over the regio- and diastereoselectivity. Highly substituted thiophenes and selenophenes are easily obtained from the generated dienes.

Conjugated dienes are relevant structural motifs due to their applications in material science and organic synthesis,[1] their prevalence in natural products,[2] and broad versatility as building blocks in a plethora of reactions,[3,4] enabling the rapid construction of molecular complexity. These features have caused a continuous interest in synthesizing 1,3-dienes.[5] Recently, stereoselective strategies for preparing highly substituted 1,3-dienes have attracted much attention.[6] Starting from alkynes, several reports have succeeded in producing conjugated dienes using palladium catalysts,[7] or bimetallic catalytic systems.[8] Migration of propargylic esters to the alkyne position followed by elimination afforded functionalized 1,3-dienes using Au- or Cu-catalysts (Scheme 1, eqn (1)),[9] or by combining both metals with hypervalent iodonium salts.[10] Also, a modular strategy for constructing 1-halo-1,3-dienes from alkynes has been described in two steps employing a copper catalyst and organolithiums (Scheme 1, eqn (2)).[11] Activated 1,3-dienes bearing heteroatomic substituents are highly relevant building blocks and, thus, a common target in synthesis.[1,12] Although less explored than their oxygenated or nitrogenated counterparts, sulfide-substituted conjugated dienes[13,14] have been acquiring interest partly due to their diverse synthetic applications like in both Diels-Alder[13] and inverse electron-demand Diels-Alder[13b] reactions after oxidation to sulfones.

In recent years, notable efforts in providing efficient routes of syntheses of these dienes have succeeded in accessing 3-substituted-(1,3-dien-2-yl)sulfanes *via* alkyne hydrothiolation followed by dehydration processes.[15] Also, Ananikov, in collaboration with König, described an elegant photocatalyzed process to synthesize precursors of activated 1,3-dienes that, upon treatment with a suitable base, release a challenging trisubstituted sulfur-activated conjugated diene (Scheme 1, eqn (3)), which could be engaged in further transformations,[16] circumventing the isolation and purification of reactive dienes.

On the other hand, sulfur migration involving alkenylation processes has experienced continuous growth,[17] arising as a powerful strategy for accessing more complex compounds like heterocycles and alkenyl sulfides. In this sense, we have recently reported the synthesis of indenes through an alkyne iodothiolation of propargylic thioethers *via* 1,3-sulfur shift (Scheme 1, eqn (4)).[18] Inspired by these findings, we envisioned that iodonium-



Scheme 1 Background, previous work and proposed tetrahydrocarbazolone synthesis from 4-(indol-2-yl)-4-oxobutanals.

Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos, Spain. E-mail: svsuarez@ubu.es

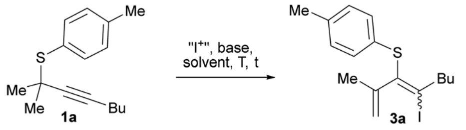
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra. See DOI: **https://doi.org/10.1039/d3cc06194a**

induced sulfur migration of propargyl thioethers could provide access to tetrasubstituted alkenes with high control on the diastereoselectivity.[19] A base could favor elimination reactions over the sulfonium intermediate **2**, enabling of highly substituted conjugated dienes bearing easily tunable halide and sulfur-based substituents (Scheme 1d).

Initially, we subjected the readily available model thioether[20] **1a** to reaction with I_2 in the presence of an external base like K_2CO_3 (Table 1), observing the formation of conjugated diene **3a** derived from alkyne activation followed by 1,2-sulfur migration only in minor amounts (entries 1 and 2). In the absence of the base starting material was recovered (entry 3). Considering the tendency of the I_2/carbonate system to afford diiodinated products with similar starting materials,[21] we tested NIS with the carbonate (entry 4). To our delight, diene **3a** was obtained in high yields as a mixture of diastereoisomers (*ca.* 4 : 1), though isomer *E* was formed preferentially. A lower base amount achieved a high yield (entry 5). Similar results were provided with catalytic amounts of DBU (entry 6). In the absence of a base (entry 7), the reaction proceeded smoothly in 30 min without observing thiochromene byproducts.[20] This result suggests that the succinimidate anion acts as a base in the elimination step. Other solvents needed higher reaction times to achieve full conversion (entries 8 and 9). Higher diastereoselectivity was obtained by lowering the temperature (entries 10 and 11). The transformation performed readily well without the base, affording almost exclusively the diene **3a** as the isomer *E* after 2 h at 0 °C (entry 10). Isomerization of diene (*E*)-**3a** may occur upon exposure to sunlight or catalytic amounts of acid, so the reactions were performed in the dark to minimize it.

Then, we investigated the scope of the reaction by applying the optimized reaction conditions to a diverse range of thioethers **1** (Table 2). Initially, we varied the substituent at R^1 linked to the S-atom that experiences the migration. Substrates bearing phenyl or different *p*- or *o*-substituted aryl groups with halogens or methoxy groups were easily transformed into corresponding dienes (**3b–f**) in high yields. Also, elevated diastereoselectivities (> 20 : 1) were observed except for products **3c** and **3f**, which required prolonged reaction times. When a naphthalene (**1g**) or different alkyl groups (**1h–k**) were installed at the S-atom, the dienes (*E*)-**3g–k** were formed with complete diastereoselectivity and good yields even when other functional groups were present in the alkyl chain (**3j** and **3k**). Though, compound **3j** was obtained in lower yields probably due to partial oxidation of the S-atom with the excess of NIS. Next, we investigated the behavior of substituents at the propargylic positions R^2 and R^3. Different cyclic, linear, or branched alkyl groups were well-tolerated, affording selectively dienes (*E*)-**3l–o** in high yields. Nevertheless, diene **3p**, in which the configuration of the tetrasubstituted alkene is fixed, was obtained as a mixture 3 : 1 of two diastereoisomers where (3*E*,5*E*)-**3p** was the major compound. Thioethers bearing unsubstituted alkynes (**1r** and **1q**) were also successfully employed. However, dienes bearing a methyl (**3r**) or a phenyl (**3q**) group at R^2 position were highly reactive, resulting in lower yields and diastereoselectivities due to rapid isomerization. Other alkyl substituents at position R^4 afforded dienes **3s** and **3t** in high yields. Notably, linear alkyl chains delivered diene **3t** as a single

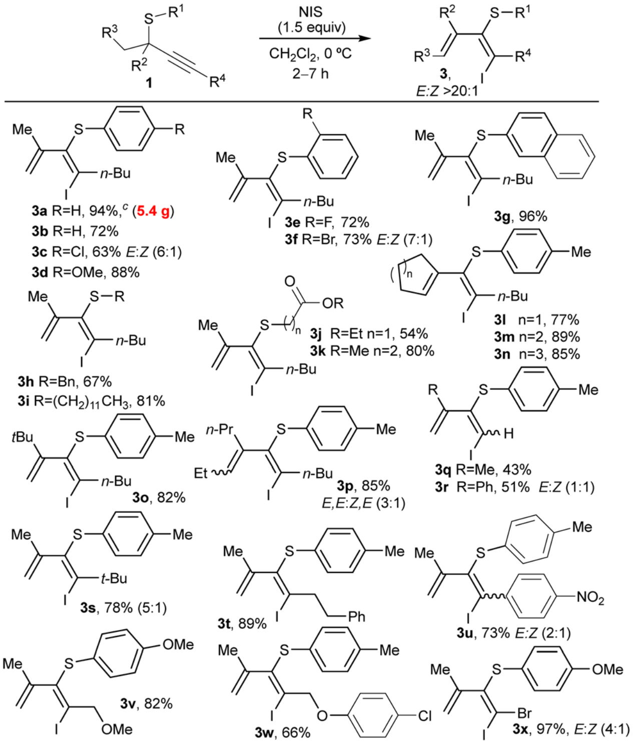
Table 1 Optimization of the reaction conditions for the synthesis of diene **3a**[a]



Entry	Solvent	I^+ source	Base	*T*	*t* (h)	**3a** Yield (%)[b] (*E* : *Z*)
1	$MeNO_2$	I_2	K_2CO_3	r.t.	6	16 (4 : 1)
2	CH_2Cl_2	I_2	K_2CO_3	r.t.	6	15 (> 20 : 1)
3	CH_2Cl_2	I_2	—	r.t.	24	—[c]
4	CH_2Cl_2	NIS	K_2CO_3	r.t.	24	92 (4.4 : 1)
5[d]	CH_2Cl_2	NIS	K_2CO_3	r.t.	24	88 (3 : 1)
6[d]	CH_2Cl_2	NIS	DBU	r.t.	24	> 95 (2 : 1)
7	CH_2Cl_2	NIS	—	r.t.	0.5	79 (2 : 1)
8	Toluene	NIS	—	r.t.	24	77 (2 : 1)
9	THF	NIS	—	r.t.	24	56 (4 : 1)
10	CH_2Cl_2	NIS	—	0 °C	2	> 95 (90)[e] (20 : 1)
11	CH_2Cl_2	NIS	K_2CO_3	0 °C	24	81 (7 : 1)[f]

[a] Reaction conditions: thioether **1a** (0.1 mmol), I^+ source (0.15 mmol), base (0.1 mmol), solvent (1 mL), temperature (*T*), and reaction time (*t*). [b] Yield determined by ^1H NMR using CH_2Br_2 as internal standard and referred to starting product **1a**. [c] Unreacted starting material **1a** was recovered. [d] The base was employed in catalytic amounts (10 mol%). [e] Yield after column chromatography referred to starting product **1a**. [f] No full conversion (86%) was observed.

Table 2 NIS-promoted synthesis of 1-iodo-1,3-dienes **3**[a,b]



[a] Reaction conditions: **1** (0.5 mmol), NIS (0.75 mmol), CH_2Cl_2 (5 mL), 0 °C, 2–7 h. [b] Yield of the isolated product. [c] Conditions: **1a** (15.5 mmol), NIS (23.2 mmol), CH_2Cl_2 (155 ml).

isomer, whereas bulky groups at R^4 like *t*-Bu (**3s**) provided lower diastereoselectivities.

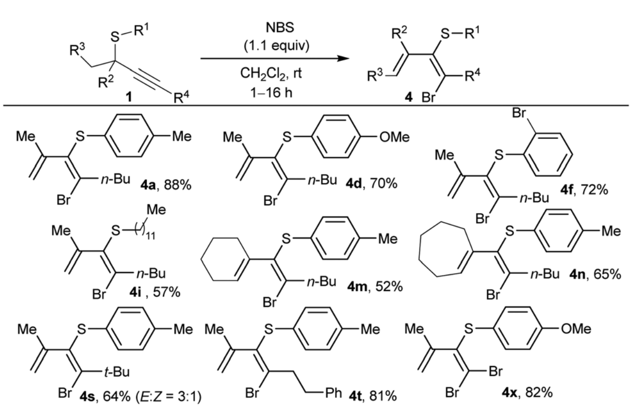
Propargylic thioethers bearing arenes directly attached at the alkyne produced the previously reported thiochromenes, except for those substrates bearing strong electron-withdrawing groups, like a *p*-nitro (**3u**), at the aromatic substituent placed at R^4. Nevertheless, lower selectivities were obtained for **3u** due to rapid isomerization in the reaction media. The reaction exhibited good compatibility with functional groups present in the alkyl chain, like, for example, methyl- or aryl ethers, that afforded the corresponding dienes **3v** and **3w**, respectively. Similarly, bromine-substituted alkyne **1x** provided the diene **3x** in almost quantitative yield as a mixture enriched in the diastereoisomer *E*. The reactions showed excellent performance at a multigram scale to obtain 5.4 g (94%) of diene **3a** with complete selectivity. By contrast, *S*-aryl secondary propargyl thioethers ($R^2 = R^3 = H$) were found to be unreactive under optimized conditions.[22]

Next, we evaluated other monopositive halonium ion sources. By using *N*-bromosuccinimide (NBS) instead of NIS, alkyne activation of **1a** followed by 1,2 sulfur migration also occurred, affording the corresponding 1-bromo-1,3-diene **4a** (Table 3). By contrast, Selectfluor or *N*-chlorosuccinimide only originated the C–S bond cleavage at the propargylic position. The excess of NBS reagent was demonstrated to be detrimental as further reactions of the generated dienes with the additional amounts of halogenating agent were observed. So, the amount of NBS was reduced to 1.1 equivalents to achieve optimal results. Then, thioethers **1** substituted at the alkyne were tested (Table 3), accessing to 1-bromo-1,3-dienes **4** in slightly lower yields than the related iododienes. Remarkably, the reaction with NBS proceeded smoothly at r.t., affording only one diastereoisomer in almost all the cases except for bulky substituent at R^4 (**4s**), with similar selectivity to that one observed with NIS to obtain **3s**. Bromodienes **4** exhibited higher stability, and no isomerization was observed upon exposure to sunlight or acids.

To further illustrate the synthetic potential of the dienes, we decided to test them as precursors in synthesizing valuable heterocycles like 3-thiorganyl substituted thiophenes and selenophenes[23] (Table 4). Conjugated iododienes **3** reacted with elemental sulfur or selenium with a copper iodide catalyst and a base, enabling a straightforward synthesis of highly substituted thiophenes and selenophenes.[24] A variety of trisubstituted thiophenes (**5a**, **5i**, **5o**, and **5t**) were obtained in high yields by reaction with elemental sulfur at 90 °C in DMF.

The reaction with pentasubstituted dienes **3n** and **3p** was demonstrated to be more challenging, although tetrasubstituted thiophenes **5n** and **5p** could also be synthesized in slightly lower yields. Regarding the synthesis of selenophenes, higher temperatures were required to accomplish an efficient heterocyclization reaction using the more stable NMP. Under these conditions, a selection of different representative selenophenes bearing three (**6a**, **6d**, and **6f**) or four substituents (**6m**) was afforded.

Table 3 NBS-promoted synthesis of 1-bromo-1,3-dienes **4**[a,b]

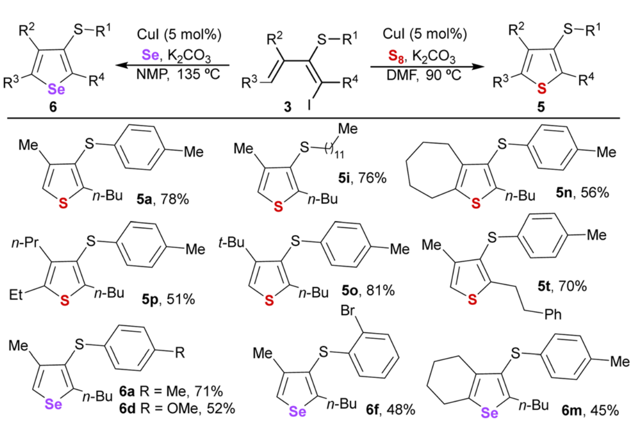


[a] Reaction conditions: **1** (0.4 mmol), NBS (0.44 mmol), CH_2Cl_2 (4 mL), rt, 1–16 h. [b] Yield of the isolated product.

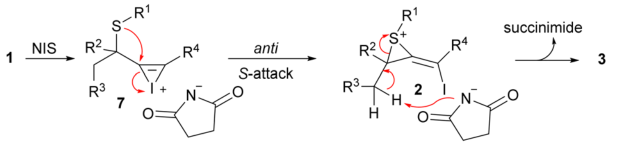
A plausible mechanism for the formation of conjugated 1-halo-1,3-dienes is depicted in Scheme 2. The interaction of thioether **1** with NIS generates cyclic iodonium intermediate **7**. Then, an *anti*-nucleophilic attack of the S-atom located at the propargylic position produces a less studied methylenethiiranium intermediate **2**.[25] The nature of R^4 substituent plays a crucial role in favoring diene formation. In this sense, alkyl, hydrogen, halogen, or electron-poor aromatics substituents prefer further evolution into sulfonium intermediate **2**, whereas electron-rich arenes could cause slippage of the iodonium ion, delivering alternative competitive thiochromene formation. Finally, conjugated iododiene **3** is released after deprotonation of the intermediate **2** by the succinimidate anion derived from the NIS.

In conclusion, a route to synthesize highly substituted conjugated dienes has been described by modulating the rich and diverse reactivity of propargylic thioethers towards alkynophilic reagents like NIS or NBS. The transformation proceeds under mild reaction conditions, enabling the formation of a variety of 1-halo-2-thio-1,3-dienes in high yields and, in general, with good control over the diastereoselectivity on the generated tetrasubstituted alkene. The process was robust enough to be performed under air and scalable. The high control over the

Table 4 Derivatization reactions of dienes **3**[a,b]



[a] Reaction conditions: **3** (0.2 mmol), S_8 or Se (0.6 mmol), CuI (5 mol%), K_2CO_3 (0.4 mmol), DMF or NMP (2 mL), 90 or 135 °C, 2 to 12 h. [b] Yield of the isolated product.



Scheme 2 Mechanistic proposal.

regio- and diastereoselectivity observed could be reasoned by a key intermediate formed after an *anti* nucleophilic S-attack to the alkyne activated by the halonium source. The choice of substrate and reaction conditions enable this 1,2-sulfur migration followed by succinimidate anion-assisted elimination sequence to obtain conjugated dienes over other alternative reactivity patterns of propargylic thioethers. The generated halodienes demonstrated potential as valuable building blocks for subsequent transformation, like synthesizing highly substituted thiophenes and selenophenes upon reaction with elemental sulfur or selenium under copper catalysis.

We gratefully acknowledge MCIN (PID2020-115789GB-C21/AEI/10.13039/501100011033), and Junta de Castilla y León and FEDER (BU028P23) for financial support. C. M.-N. thanks Junta de Castilla y León and Fondo Social Europeo, for a predoctoral contract. S. S.-P. thanks a Ramón y Cajal (RYC2021-031533-I) contract by MCIN/AEI/10.13039/501100011033 and European Union "NextGenerationEU"/PRTR.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 Z. Rappoport, *PATAI'S Chemistry of Functional Groups: The Chemistry of Dienes and Polyenes*, Wiley, 2000, vol. 2.

2 S. D. Rychnovsky, *Chem. Rev.*, 1995, **95**, 2021–2040.

3 K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2002, **41**, 1668–1698.

4 (*a*) J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, *Chem. Rev.*, 2015, **115**, 5301–5365; (*b*) G. J. P. Perry, T. Jia and D. J. Procter, *ACS Catal.*, 2020, **10**, 1485–1499.

5 (*a*) M. De Paolis, I. Chataigner and J. Maddaluno, in *Stereoselective Alkene Synthesis*, ed. J. Wang, Springer Berlin Heidelberg, 2012, pp. 87–146; (*b*) P. Hubert, E. Seibel, C. Beemelmanns, J.-M. Campagne and R. M. de Figueiredo, *Adv. Synth. Catal.*, 2020, **362**, 5532–5575; (*c*) R. G. Soengas and H. Rodríguez-Solla, *Molecules*, 2021, **26**, 249.

6 (*a*) S. Manna, S. Paul, W.-Y. Kong, D. Aich, R. Sahoo, D. J. Tantillo and S. Panda, *Angew. Chem., Int. Ed.*, 2023, **62**, e202309136; (*b*) W.-J. Kong, S. N. Kessler, H. Wu and J.-E. Bäckvall, *Org. Lett.*, 2023, **25**, 120–124; (*c*) G.-X. Liu, X.-T. Jie, X.-l Li, L.-S. Yang, H. Qiu and W.-H. Hu, *ACS Catal.*, 2023, **13**, 5307–5314; (*d*) W.-S. Zhang, D.-W. Ji, Y. Li, X.-X. Zhang, Y.-K. Mei, B.-Z. Chen and Q.-A. Chen, *Nat. Commun.*, 2023, **14**, 651; (*e*) R.-P. Li, J. Li, X. Chen, J. Liu, X. Wang and S. Tang, *Adv. Synth. Catal.*, 2022, **364**, 4260–4265.

7 (*a*) N. J. Green, A. C. Willis and M. S. Sherburn, *Angew. Chem., Int. Ed.*, 2016, **55**, 9244–9248; (*b*) J. Liu, J. Yang, W. Baumann, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2019, **58**, 10683–10687; (*c*) X.-B. Xiang, S. Wang, T. Xu and S. Chen, *Org. Lett.*, 2023, **25**, 587–591.

8 (*a*) T. Long, C. Zhu, L. Li, L. Shao, S. Zhu, M. Rueping and L. Chu, *Nat. Commun.*, 2023, **14**, 55; (*b*) C.-J. Hou, A. W. Schuppe, J. L. Knippel, A. Z. Ni and S. L. Buchwald, *Org. Lett.*, 2021, **23**, 8816–8821.

9 R. Kazem Shiroodi, A. S. Dudnik and V. Gevorgyan, *J. Am. Chem. Soc.*, 2012, **134**, 6928–6931.

10 Z. Sun, M. Dai, C. Ding, S. Chen and L.-A. Chen, *J. Am. Chem. Soc.*, 2023, **145**, 18115–18125.

11 E. Rivera-Chao and M. Fañanás-Mastral, *Angew. Chem., Int. Ed.*, 2021, **60**, 16922–16927.

12 A. Deagostino, C. Prandi, C. Zavattaro and P. Venturello, *Eur. J. Org. Chem.*, 2006, 2463–2483.

13 (*a*) F. Peng, R. E. Grote, R. M. Wilson and S. J. Danishefsky, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, **110**, 10904–10909; (*b*) J. Choi, H. Park, H. J. Yoo, S. Kim, E. J. Sorensen and C. Lee, *J. Am. Chem. Soc.*, 2014, **136**, 9918–9921.

14 (*a*) J.-E. Bäckvall and A. Ericsson, *J. Org. Chem.*, 1994, **59**, 5850–5851; (*b*) S. S. Zalesskiy, N. S. Shlapakov and V. P. Ananikov, *Chem. Sci.*, 2016, **7**, 6740–6745.

15 E. S. Degtyareva, E. V. Borkovskaya and V. P. Ananikov, *ACS Sustainable Chem. Eng.*, 2019, **7**, 9680–9689.

16 J. V. Burykina, A. D. Kobelev, N. S. Shlapakov, A. Y. Kostyukovich, A. N. Fakhrutdinov, B. König and V. P. Ananikov, *Angew. Chem., Int. Ed.*, 2022, **61**, e202116888.

17 For 1,2 sulfur migration, see: (*a*) J. T. Kim, A. V. Kel'in and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2003, **42**, 98–101; (*b*) A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel'in and V. Gevorgyan, *J. Am. Chem. Soc.*, 2008, **130**, 1440–1452; (*c*) L. Peng, X. Zhang, S. Zhang and J. Wang, *J. Org. Chem.*, 2007, **72**, 1192–1197; (*d*) T. Yuan, B. Ryckaert, K. Van Hecke, J. Hullaert and J. M. Winne, *Angew. Chem., Int. Ed.*, 2021, **60**, 4070–4074. For 1,3 sulfur migration, see: (*e*) S. B. Wagh, R. R. Singh, R. L. Sahani and R.-S. Liu, *Org. Lett.*, 2019, **21**, 2755–2758. For 1,4 sulfur migration, see: (*f*) J. A. Kaplan, A. Issaian, M. Stang, D. Gorial and S. A. Blum, *Angew. Chem., Int. Ed.*, 2021, **60**, 25776–25780; (*g*) F. Martínez-Lara, A. Suárez, N. Velasco, S. Suárez-Pantiga and R. Sanz, *Adv. Synth. Catal.*, 2022, **364**, 132–138. For related halogen-induced 1,2-migrations of heteroatoms, see also: (*h*) D.-H. Tan, Z.-H. Chen, L. Yang, C.-T. Li, F.-H. Tu, Q. Li and H. Wang, *Sci. China Chem.*, 2022, **65**, 746–752; (*i*) F.-H. Tu, Y. Wang, Z. Li, S. Yang, Y. Li, D.-H. Tan, Q. Li, H. Gao and H. Wang, *Cell Rep. Phys. Sci.*, 2022, **3**, 101194.

18 N. Velasco, C. Martínez-Núñez, M. A. Fernández-Rodríguez, R. Sanz and S. Suárez-Pantiga, *Adv. Synth. Catal.*, 2022, **364**, 2932–2938.

19 A. N. V. Satyanarayana, N. Mukherjee and T. Chatterjee, *Green Chem.*, 2023, **25**, 779–788.

20 N. Velasco, A. Suárez, F. Martínez-Lara, M. Á. Fernández-Rodríguez, R. Sanz and S. Suárez-Pantiga, *J. Org. Chem.*, 2021, **86**, 7078–7091.

21 F. Yang, T.-N. Jin, M. Bao and Y. Yamamoto, *Tetrahedron Lett.*, 2011, **52**, 936–938.

22 For further details, see ESI†.

23 (*a*) M. Wang, Q. Fan and X. Jiang, *Org. Lett.*, 2016, **18**, 5756–5759; (*b*) M. Wang, J. Wei, Q. Fan and X. Jiang, *Chem. Commun.*, 2017, **53**, 2918–2921. For some applications of 3-thiorganyl thiophenes and selenophenes in material science, see: (*c*) R. Cagnoli, M. Lanzi, E. Libertini, A. Mucci, L. Paganin, F. Parenti, L. Preti and L. Schenetti, *Macromolecules*, 2008, **41**, 3785–3792; (*d*) Y. H. Wijsboom, Y. Sheynin, A. Patra, N. Zamoshchik, R. Vardimon, G. Leitus and M. Bendikov, *J. Mat. Chem.*, 2011, **21**, 1368–1372. For application in drugs, see: (*e*) D. Tondi, R. A. Powers, E. Caselli, M. a-C. Negri, J. Blázquez, M. P. Costi and B. K. Shoichet, *Chem. Biol.*, 2001, **8**, 593–610.

24 (*a*) B. Wu and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 10496–10499; (*b*) J. Wu and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2016, **55**, 336–340.

25 For related intermediates employing gold catalysts, see also: ref. 17c and d.