Organic & Biomolecular Chemistry

This article can be cited before page numbers have been issued, to do this please use: E. P. Urriolabeitia and S. Ruiz, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C8OB03201G.

Volume 14 | Number 1 | 7 January 2016 | Pages 1–372

Organic & Biomolecular Chemistry

www.rsc.org/obc

ISSN 1477-0520

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION
Takeharu Haino et al.
Solvent-induced emission of organogels based on tris(phenylisoxazolyl)benzene

175 YEARS

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB03201G

Journal Name

ARTICLE

Ru(II)-catalysed synthesis of (1*H*)-isothiochromenes by oxidative coupling of benzylthioethers with internal alkynes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Esteban P. Urriolabeitia,*[a] and Sara Ruiz [a]

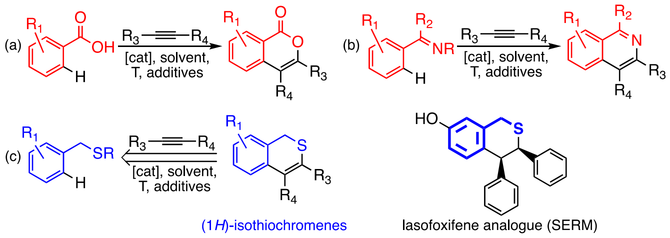
The synthesis of 1*H*-isothiochromenes by oxidative coupling of benzyl(*tert*-butyl)thioethers with internal alkynes, catalysed by Ru(II), has been achieved. The reaction occurs by S-directed C-H activation at the *ortho* position of the aryl ring, promoted by ruthenium, migratory insertion of the alkyne, 1,2-thio-Wittig rearrangement of the *tert*-butyl group and reductive elimination by C-S coupling between the resulting anionic sulfide and the vinylic carbon

Introduction

The transition metal-catalysed oxidative functionalization of C-H bonds is at present a well consolidated synthetic tool in organic chemistry.[1,2] In particular, the synthesis of heterocycles by oxidative coupling of arenes or heteroarenes with internal alkynes has experienced an impressive development.[3] Key features of these processes are the use of catalytic amounts of metals, mild reaction conditions and high regio- and stereo-selectivity, achieved using directing groups (DG). In addition, when the process is designed to incorporate the DG into the target molecule, a complete atom economy can be attained, minimizing synthetic steps and waste materials, and saving time, resources and energy. Relevant examples are the synthesis of isocoumarins or isoquinolines from coupling of internal alkynes with, respectively, carboxylic acids (Scheme 1a) and amines or imines (Scheme 1b).[3]

A detailed inspection of the literature in this area shows that O- or N-based DGs are almost ubiquitous, while other heteroatoms with good bonding ability are underrepresented. The use of S-directing groups in the synthesis of S-heterocycles is a paradigm of the latter statement, because few examples are known. Probably, the high affinity of transition metals to bind to sulfur is the responsible for this shortage of examples, because a strong M-S bond would form stable complexes, promoting the poisoning and deactivation of the catalyst.[4]

The interest on sulfur heterocycles resides on their recognized biological and pharmacological activity,[5] their presence in agrochemical compounds,[5] in materials with useful optical and electronic properties, or as valuable synthetic intermediates or ligands.[6] More specifically, the (1*H*)-isothiochromenes such as the lasofoxifene and its analogues (Scheme 1c) are selective estrogen receptor modulators (SERMs),[7a] active compounds in the osteoporosis treatment,[7b] and behave as analogs of isocoumarins in the cancer treatment.[7c] According to the retrosynthesis shown in Scheme 1c, the oxidative coupling between a thioether and an internal alkyne through C-H activation could be the shortest and most efficient synthetic pathway to this class of compounds but, as far as we know, it is still unknown.



Scheme 1. Synthesis of isocoumarins (a) and isoquinolines (b) from carboxylic acids and imines. Retrosynthesis of (1*H*)-isothiochromenes (c) and a representative example.

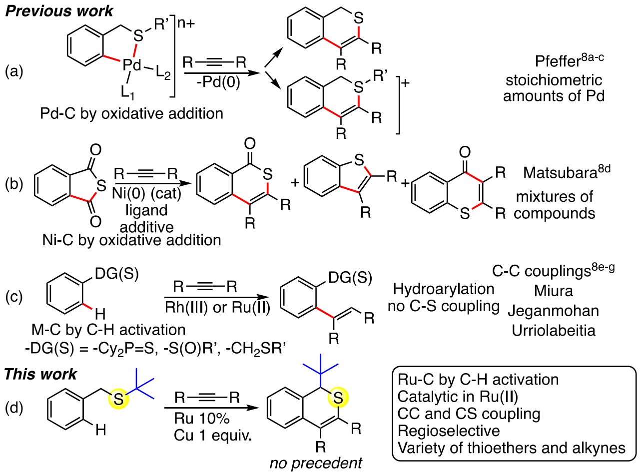
Previous work in metal-mediated synthesis of (1*H*)-isothiochromenes by coupling of arenes and alkynes started with the work of Pfeffer et al., where orthopalladated thiothers were reacted with internal alkynes under harsh conditions to give thiopyranes, thiepins and related species (Scheme 2a).[8a-c] This method proved to be versatile, but consumed stoichiometric amounts of Pd. The reaction of thiophthalic anhydride with alkynes catalysed by Ni^0 provides an additional route (Scheme 2b), but needs harsh reaction conditions and specific combinations of solvents and additives, otherwise mixtures of compounds were obtained.[8d] The reaction of internal alkynes with aryl rings containing S-directing groups, such as phosphine sulfides,[8e] sulfoxides,[8f] or thioethers,[8g] gives only *ortho*-alkenylated derivatives by hydroarylation, (Scheme 2c). Due to the interest of (1*H*)-isothiochromenes and the lack of simple and efficient preparative routes,[9] we have investigated this area, following previous related research.[8g] We report here the synthesis of (1*H*)-isothiochromenes by Ru-

---

[a] *Instituto de Síntesis Química y Catálisis Homogénea, ISQCH, CSIC-Universidad de Zaragoza, Pedro Cerbuna 12, 50009 Zaragoza (Spain)*

Electronic Supplementary Information (ESI) available: [Complete experimental section, characterization data and NMR spectra of all compounds; optimization of compound 3aa]. See DOI: 10.1039/x0xx00000x.

catalysed oxidative coupling of benzyl(*tert*-butyl) thioethers with internal alkynes (Scheme 2d).



Scheme 2. Previous and present work on synthesis of (1*H*)-isothiochromenes.

Results and discussion

We have selected as model substrate the benzyl(*tert*-butyl) thioether **1a**, because it showed an excellent reactivity in hydroarylation reactions.[8g] Moreover, we expect that the *tert*-butyl group could be eliminated as isobutene and H^+,[8a] generating a nucleophilic thiolate, more prone to give the C-S coupling than the neutral thioether. Other thioethers **1a-1n** were prepared from ^{t}BuSH and the substituted benzylbromides, using a phase transfer agent in basic medium (see ESI for details).

We started the optimization of this reaction from the conditions reported for hydroarylation of thioethers: 1 mmol thioether **1a**, 2 mmol alkyne **2a**, 10% mol Ru catalyst, 10% mol KPF_6, 1 mmol $Cu(OAc)_2$, hexafluoroisopropanol (HFIP) as solvent, 100 °C, 24 h.[8g] Under these conditions, only the hydroarylation product **4aa** was obtained (Scheme 3a). According to our previously reported mechanism, after C-H bond activation of the thioether and migratory insertion of the alkyne, a protodemetalation step occurs due to the acetic acid generated after the C-H bond activation.[8g] It seems sensible to assume that the removal of the acid, performing the reaction in the presence of base, would disfavour the protodemetalation allowing the C-S coupling. In fact, when the reaction between **1a** and **2a** was performed at 100 °C in presence of 1 mmol of K_2CO_3 the formation of **4aa** decreased notably to a 36%, while the formation of a new product **3aa** in 57% yield was evident. The full details of the optimization procedure are given in the ESI. Despite this initial result, and after exhaustive screening of reaction conditions, we found that a decrease of the reaction temperature to 60 °C allowed the selective formation of **3aa**, surprisingly without the need of additional base. This suggests that the synthesis of **3aa** or **4aa** from the same precursors is a problem of kinetic nature. The complete characterization of **3aa** and, in general, of compounds type **3**, required the combined use of spectroscopic and diffraction techniques. We succeeded obtaining single crystals of **3ba** (from **1b** and **2a**, see Scheme 4 and ESI), which were adequate for X-ray diffraction. The molecular structure of **3ba** is shown in Figure 1, and shows an isothiochromene or benzothiopyrane bicyclic molecule, that is, a phenyl ring fused to a thiopyrane ring, which is substituted in positions 3 and 4 by ethyl groups and in position 1 by the *tert*-butyl group. This means that, in addition to the expected *ortho*-activation of the thioether and migratory insertion of the alkyne, an unexpected migration of the *tert*-butyl group from the sulfur to the C1 has taken place, as well as the desired formation of the C-S bond. The bond distances and angles of this structure are identical, within experimental error, to those observed in the few examples found in the literature.[8a]

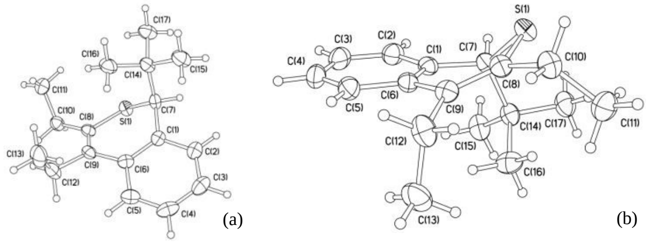
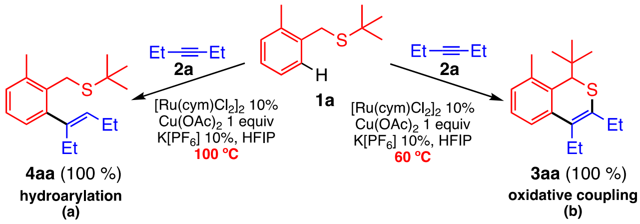


Figure 1. Thermal ellipsoid plot of isothiochromene **3ba**: (a) top view and (b) side view



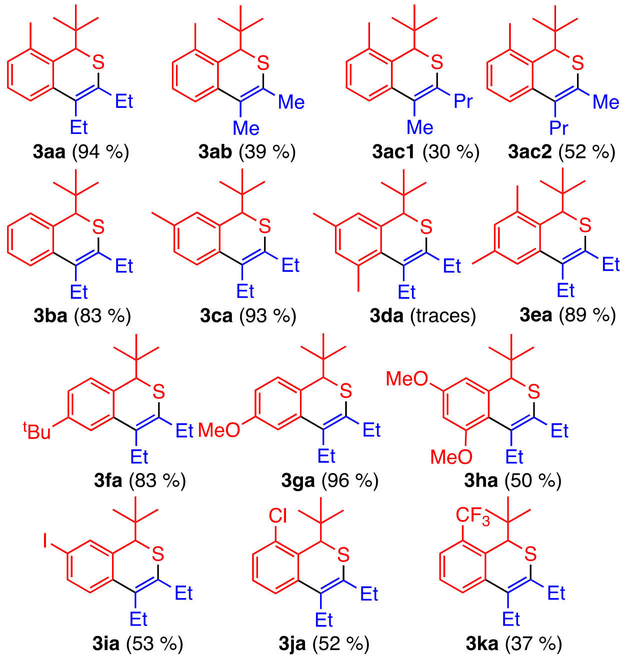
Scheme 3. Condensed optimization of the synthesis of 3aa

Once the reaction has optimized conditions, the scope of the reaction was checked. Good isolated yields were achieved with electron-rich alkynes, such as 3-hexyne, 2-butyne or 2-hexyne (Scheme 4), obtaining the isothiochromenes **3aa**, **3ab** and **3ac** in 94%, 39% and 82% isolated yields, respectively. As for **3ab** the moderate yield was due to purification problems, because the hydroarylation by-product **4ab** (also obtained in this case) was difficult to separate by column chromatography. In the case of 2-hexyne, **3ac** was obtained as the mixture of the two regioisomers. The reactivity of electron-poor alkynes is more restricted, as alkynes containing ester groups showed to be unreactive, while alkynes containing aryl groups gave low conversions and the corresponding derivatives could not be isolated in pure form.

The reaction shows a high tolerance to the presence of functional groups on the benzyl fragment. First, we have checked if poly-insertion of alkynes can occur, as observed in hydroarylation reactions.[8g] The unsubstituted thioether **1b** reacts with **2a** under the optimized conditions to give selectively the mono-inserted derivative **3ba** (Scheme 4) whose X-ray crystal structure was determined (Figure 1). Even if the reaction is performed using an excess of alkyne, the bis-insertion product

View Article Online
DOI: 10.1039/C8OB03201C

was not detected. Therefore, this method is not restricted to the use of *ortho*-substituted precursors, allowing a wide prospect of starting materials. In addition, only the *ortho*-position of the benzyl ring was activated, meaning that the reaction takes place regioselectively due to the S-directing effect.

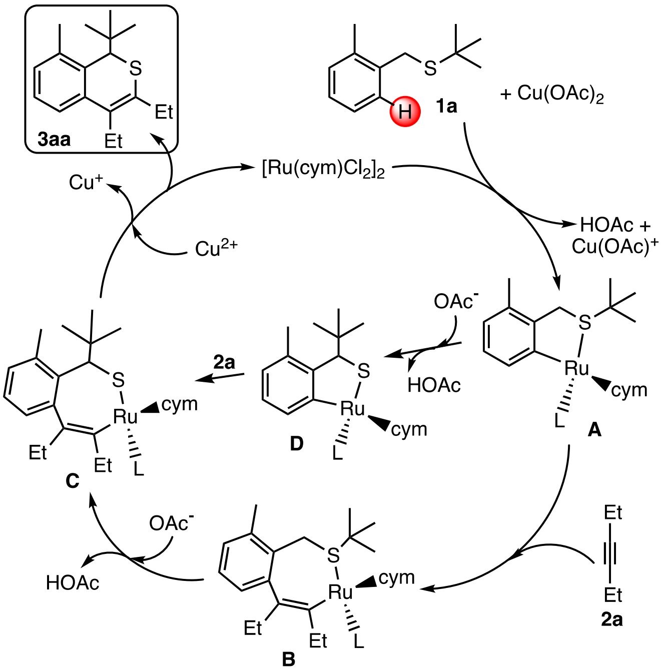


Scheme 4. Scope of the synthesis of (1*H*)-isothiochromenes

The thioether **1c**, containing a methyl group at 3-position, gives **3ca** with complete regioselectivity, showing that the less sterically hindered 6-position was activated. It seems that the activation of the 2-position in the thioether when a substituent is present at 3-position is strongly inhibited. Thus, the reaction of the 3,5-dimethyl substituted thioether **1d** with **2a** affords **3da** only as traces, because both positions (2 and 6) are hindered. However, **1e**, containing two methyl substituents at 2 and 4 positions, gives **3ea** in good yield (89%) by selective activation at the 6-position, while the 4-ᵗBu substituted **1f** affords **3fa** in 83% yield.

Strongly electron-donating groups such as -OMe have a beneficial effect for the synthesis of the isothiochromenes. The reaction between the 4-OMe substituted thioether **1g** with **2a** gives **3ga** in an excellent 96% isolated yield. Moreover, the reaction of the 3,5-dimethoxy thioether **1h** with **2a** gives **3ha** in a moderate 50% yield, meaning that the detrimental effect of the steric hindrance can be counterbalanced by the activating electronic effects exerted by strong electron-donating groups. On the other hand, the substitution of the phenyl ring with electron-withdrawing groups is also tolerated, although a slight decrease in the reaction yield is observed. Thus, synthetically useful groups such as iodide (**3ia**) and chloride (**3ja**) can be kept during the reaction, giving the corresponding heterocycles in yields around 53% (Scheme 4). It is remarkable that the formation of the iodine derivative **3ia** is totally regioselective, obtaining the isomer with the iodine in 7-position. When the electron-withdrawing ability of the substituent increases, for instance when a 2-CF_3 unit is employed, the isothiochromene **3ka** is still obtained, but the isolated yield drops to 37%. When thioethers containing nitro groups as **1l** or **1n** were used (ESI), only hydroarylation derivatives were obtained, while the isothiochromenes were not detected. While the reaction tolerates different substituents at the alkyne and the benzyl fragment of the thioether, it seems quite selective with respect to the S-substituent. In fact, when the starting benzylthioether contains other bulky groups at the S atom (for instance *iso*-propyl or cyclohexyl) instead of the *tert*-butyl group, the formation of the isothiochromene was not detected and only the hydroarylation reaction is observed.

From the mechanistic point of view, we propose tentatively that the reaction starts by coordination of thioether **1a** to $Cu(OAc)_2$, as previously described (Scheme 5).[8g]



Scheme 5. Proposed catalytic cycle for the synthesis of (1*H*)-isothiochromenes

From the Cu center, both the thioether and one acetate can be transmetallated to Ru, where C-H activation at the *ortho*-position of the aryl ring takes place giving cycloruthenated **A**. Intermediate **A** can then follow two different pathways. In the first one (lowest part of Scheme 5), bonding of the alkyne and further migratory insertion affords vinyl intermediate **B**. Then, reductive elimination from **B** does not explain the formation of isothiochromenes **3**, because a migration of the *tert*-butyl group from the sulfur to the Cα has to take place. The migration of the *tert*-butyl group from the sulfur to the alpha carbon can be formally considered a 1,2-thio-Wittig rearrangement, a reaction often found in ethers and thioethers, which occurs in the presence of base and gives alcohols and thiols, respectively.[10] The mechanism of the [1,2]-Wittig rearrangement has been subject of extensive discussion, but it seems well-established now that it takes place *via* a radical dissociation-recombination

View Article Online
DOI: 10.1039/C8OB03201G

mechanism.[10] Therefore, intermediate **C** is formed after the Wittig migration. From **C**, containing a nucleophilic sulphide, a reductive elimination could take place, giving Ru(0) and isothiochromenes **3**. The Ru(II) species are regenerated by oxidation with Cu(II), closing the catalytic cycle. In the second possibility (middle part, Scheme 5), intermediate **A** undergoes thio-Wittig rearrangement before alkyne insertion, affording species **D**. Alkyne bonding to **D** and further migratory insertion affords **C**, which evolves as discussed in the previous paragraph. The exact point of the catalytic cycle at which the thio-Wittig rearrangment takes place (**A** or **B**) remains speculative. We know that it can't occur before the C-H activation step, that is, before the formation of species **A**, because the reactivity of thiolates with internal alkynes in the presence of $Cu(OAc)_2$ has been recently reported and follows a totally different pathway, not observed here.[11] Thus, it can occur either after the C-H bond activation in **A**, giving cycloruthenated **D**, which affords **C** by migratory insertion of **2a**, or in vinyl intermediate **B** to give **C**. Attempts to isolate cycloruthenated **A** were not successful, therefore details of the reactivity of **A** are not accessible.

Experimental

General methods

All reactions were carried out in Young's flasks, without protecting atmosphere. Solvents were used as received from commercial sources: they were not distilled nor subjected to additional purification. Flash column liquid chromatographies were performed on aluminium oxide 90 neutral (50-200 μm) or silica gel (70-230 μm). ^{1}H and ^{13}C NMR spectra were all recorded in $CDCl_3$ or acetone-d_6 solutions at 25 °C on Bruker AV500, AV400 or AV300 spectrometers (δ in ppm, *J* in Hz) at ^{1}H operating frequencies of 500.13, 400.13 or 300.13 MHz, respectively, and were referenced using the solvent signal as internal standard. HRMS and ESI (ESI+) mass spectra were recorded using an MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 m/z and mass resolution 15000 (FWHM). Some products could not be adequately characterized by high-resolution MS. In these cases, elemental analyses (CHNS) were provided instead, which were performed on a PerkinElmer 2400 Series II microanalyser. The synthesis of $[Ru(p\text{-cymene})Cl_2]_2$ has been carried out following published procedures.[12]

X-Ray crystallography. Crystal structure determination of 3ba

Crystals of compound **3ba** of adequate quality for X-ray measurements were grown from slow evaporation of a $CHCl_3$ solution of the crude compound at room temperature. A single crystal was mounted at the end of a quartz fiber in a random orientation, covered with perfluorinated oil and placed under a cold stream of N_2 gas. The X-ray data collection was performed on an Oxford Diffraction Xcalibur2 diffractometer using graphite-monochromated Mo-Kα (λ = 0.71073 Å). A hemisphere of data was collected based on ω-scan or ϕ-scan runs. The diffraction frames were integrated using the program CrysAlis RED[13] and the integrated intensities were corrected for absorption with SADABS.[14] The structures were solved and developed by Patterson and Fourier methods.[15] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were placed at idealized positions and treated as riding atoms. Each H atom was assigned an isotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of its parent atom. The structures were refined to F_o^2 and all reflections were used in the least-squares calculations.[16] Crystallographic data (including structure factors) for the structure of **3ba** had been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1544460. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Preparation and characterization of starting materials. General procedure for the synthesis of *tert*-butyl thioethers 1a-1n

Starting thioethers (**1a-1n**) were synthetized as follows. To a mixture of the corresponding benzylbromide (2.5 mmol), aliquat (50 mg, 0.12 mmol) and NaOH (225 mg, 5.6 mmol) in toluene/water (2.5:2.5 mL), *tert*-butylthiol (2.5 mmol) was added dropwise. The resulting mixture was stirred for 1 h at 25 °C. After this time, the reaction was quenched by addition of HCl 1M (10 mL), then extracted with Et_2O (2×10mL). The organic phase was washed with brine (5×30 mL), dried over $MgSO_4$ and evaporated to dryness to yield the pure products as oils. The characterization of **1a** is shown here. The characterization of the remaining compounds **1b-1n** is given as ESI.

1a (*tert*-butyl(2-methylbenzyl)sulfane): dark yellow oil (427 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (m, 1H, C_6H_4), 7.02 (m, 3H, C_6H_4), 3.63 (s, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.29 (s, 9H, $C(CH_3)_3$). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ = 136.7 (C), 135.9 (C), 130.5 (CH), 129.9 (CH), 127.2 (CH), 126.1 (CH), 42.7 (C), 31.2 (CH_2), 30.8 (CH_3), 19.1 (CH_3). Anal. Calcd for $C_{12}H_{18}S$: C, 74.17; H, 9.34; S, 16.50. Found: C, 73.95; H, 9.05; S, 16.80.

General procedure for the catalytic coupling of benzylthioethers 1 with alkynes 2

To a suspension of $[RuCl_2(p\text{-cymene})]_2$ (61.2 mg, 0.1 mmol), $K[PF_6]$ (18.7 mg, 0.1 mmol) and $Cu(OAc)_2$ (181.6 mg, 1 mmol) in HFIP (3 mL), the corresponding thioether **1** (1 mmol) and internal alkyne **2** (2 mmol) were added. The reaction mixture was stirred for 24 h at 60 °C. After the reaction time the solvent was evaporated to dryness, the residue was dissolved in CH_2Cl_2 and purified by flash column chromatography using neutral alumina as support and CH_2Cl_2 as eluent. The collected fraction was evaporated to dryness and the oily residue was further purified by column chromatography using silica gel as support and a mixture of Et_2O/hexane as eluent, affording isothiochromenes (**3**) as yellow oils, which solidifed on standing in most of the cases. . The characterization of **3aa** is shown here. The characterization of the remaining isothiochromenes is given in the ESI.

3aa (1-(*tert*-butyl)-3,4-diethyl-8-methyl-1*H*-isothiochromene): yellow waxy solid (258 mg, 94 %). Purified by column chromatography on silica gel, eluting with hexane/Et_2O 99:1. ^{1}H NMR (300 MHz, acetone-d_6): δ = 7.35 (m, 1 H, C_6H_3), 7.17 (m, 2 H, C_6H_3), 3.94 (s, 1H, CH), 2.68 (m, 3H, CH_2CH_3), 2.42 (s, 3H, CH_3),

View Article Online
DOI: 10.1039/C8OB03201G

2.17 (m, 1H, CH_2CH$_3$), 1.26 (t, 3H, CH$_2$CH_3, $^3J_{HH}$ = 7.5 Hz), 1.16 (t, 3H, CH$_2$CH_3, $^3J_{HH}$ = 7.5 Hz), 0.93 (s, 9H, C-(CH$_3$)$_3$). ^{13}C{^{1}H} NMR (75 MHz, acetone-*d*^{6}): δ = 135.6 (C), 135.1 (C), 131.7 (C), 130.5 (C), 129.3 (CH), 128.1 (C), 126.0 (CH), 121.5 (CH), 46.4 (CH), 39.4 (C), 27.1 (CH$_2$), 26.8 (CH$_3$), 21.4 (CH$_2$), 20.5 (CH$_3$), 13.5 (CH$_3$). HRMS (ESI-TOF) *m/z:* [M+Na+O]$^+$ calcd for $C_{18}H_{26}NaOS$ 313.1597, obtained 313.1588.

Conclusions

In conclusion, we have developed for the first time a catalytic method for the synthesis of (1*H*)-isothiochromenes involving C-C and C-S bond formation, providing a synthetic disconnection not previously reported. The method is based on the oxidative coupling of a benzylthioether with an internal alkyne, and takes place in one pot through regioselective Ru-catalysed C-H activation of the thioether, migratory insertion of the alkyne, 1,2-thio-Wittig rearrangement of the *tert*-butyl group and C-S bond formation by reductive elimination. This method represents a substantial improvement with respect to previous methods, and provides a wide scope of application.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

E.P.U. thanks the European Cooperation in Science and Technology (COST) program under CA15106 grant (CHAOS: CH Activation in Organic Synthesis) and Gobierno de Aragón-FEDER (Spain, research group E19_17R: Aminoácidos y Péptidos) for financial support. S. R. thanks Gobierno de Aragón for a PhD fellowship.

Notes and references

1 *Catalytic Transformations via C-H Activation*, volumes 1 and 2; J.-Q. Yu, Editor; Science of Synthesis, Georg Thieme Verlag KG, Stuttgart, Germany, 2016.

2 (a) C-H Bond Activation and Catalytic Functionalization I, P. H. Dixneuf and H. Doucet, Editors, *Top. Organomet. Chem.* 2016, **55**, 1-260; (b) C-H Bond Activation and Catalytic Functionalization II, P. H. Dixneuf and H. Doucet, Editors, *Top. Organomet. Chem.* 2016, **56**, 1-264; (c) F. Roudesly, J. Oble and G. Poli, *J. Mol. Catal. A: Chem.* 2017, **426**, 275; (d) J. F. Hartwig, *J. Am. Chem. Soc.* 2016, **138**, 2; (e) J. J. Topczewski and M. S. Sanford, *Chem. Sci.* 2015, **6**, 70; (f) O. Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.* 2015, **48**, 1053; (g) G. Shi and Y. Zhang, *Adv. Synth. Catal.* 2014, **356**, 1419; (h) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.* 2013, **52**, 11726; (i) J. Wencel-Delord and F. Glorius, *Nature Chem.* 2013, **5**, 369; (j) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.* 2012, **45**, 788; (k) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.* 2011, **40**, 1976; (l) L. Ackermann, *Chem. Rev.* 2011, **111**, 1315; (m) K. M. Engle, T.-S. Mei, X. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.* 2011, **50**, 1478; (n) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.* 2010, **110**, 624. (o) T. W. Lyons and M. S. Sanford, *Chem. Rev.* 2010, **110**, 1147.

3 (a) L. Ackermann, *Acc. Chem. Res.* 2014, **47**, 281; (b) M. Gulías and J. L. Mascareñas, *Angew. Chem. Int. Ed.* 2016, **55**, 11000; (c) V. P. Boyarskiy, D. S. Ryabukhin, N. A. Bokach and A. V. Vasilyev, *Chem. Rev.* 2016, **116**, 5894; (d) S. Ruiz, P. Villuendas and E. P. Urriolabeitia, *Tetrahedron Lett.* 2016, **57**, 3413; (e) X.-X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.* 2015, **115**, 1622; (f) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.* 2015, **2**, 1107; (g) S. de Sarkar, W. Liu, S. Kozhushkov and L. Ackermann, *Adv. Synth. Catal.* 2014, **356**, 1461; (h) R. He, Z.-T. Huang, Q.-Y. Zheng and C. Wang, *Tetrahedron Lett.* 2014, **55**, 5705; (i) Y. Yamamoto, *Chem. Soc. Rev.* 2014, **43**, 1575; (j) R. Chinchilla and C. Nájera, *Chem. Rev.* 2014, **114**, 1783; (k) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.* 2012, **41**, 3651; (l) T. Satoh and M. Miura, *Chem. Eur. J.* 2010, **16**, 11212; (m) M. Zhang, *Adv. Synth. Catal.* 2009, **351**, 2243; (n) P. Thansandote and M. Lautens, *Chem. Eur. J.* 2009, **15**, 5874.

4 (a) C. C. Eichman and J. P. Stambuli, *J. Org. Chem.* 2009, **74**, 4005; (b) J. K. Dunleavy, *Platinum Met. Rev.* 2006, **50**, 110.

5 (a) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.* 2014, **57**, 2832; (b) H. Haruki, M. G. Pedersen, K. I. Gorska, F. Pojer and K. Johnsson, *Science* 2013, **340**, 987; (c) T. Mendgen, C. Steuer and C. D. Kelin, *J. Med. Chem.* 2012, **55**, 743; (d) P. Martins, J. Jesus, S. Santos, L. R. Raposo, C. Roma-Rodrigues, P. V. Baptista and A. R. Fernandes, *Molecules* 2015, **20**, 16852; (e) M. D. McReynolds, J. M. Dougherty and P. R. Hanson, *Chem. Rev.* 2004, **104**, 2239.

6 (a) A. R. Murphy and J. M. J. Fréchet, *Chem. Rev.* 2007, **107**, 1066; (b) M. Mellah, A. Voituriez and E. Schulz, *Chem. Rev.* 2007, **107**, 5133.

7 (a) J. Liu, E. T. Birzin, W. Chan, Y. T. Yang, L. Y. Pai, C. DaSilva, E. C. Hayes, R. T. Mosley, F. DiNinno, S. P. Rohrer, J. M. Schaeffer and M. L. Hammond, *Biorg. Med. Chem. Lett.* 2005, **15**, 715; (b) T. Oda, K. Notoya, M. Gotoh, S. Taketomi, Y. Fujisawa, H. Makino and T. Sohda, *J. Med. Chem.* 1999, **42**, 751; (c) D. Kaminskyy, A. Kryshchyshyn, I. Nektegayev, O. Vasylenko, P. Grellier and R. Lesyk, *Eur. J. Med. Chem.* 2014, **75**, 57.

8 (a) J. Spencer, M. Pfeffer, A. DeCian and J. Fischer, *J. Org. Chem.* 1995, **60**, 1005; (b) J. Spencer, M. Pfeffer, N. Kyritsakas and J. Fischer, *Organometallics* 1995, **14**, 2214; (c) J. Dupont and M. Pfeffer, *J. Organomet. Chem.* 1987, **321**, C13; (d) T. Inami, Y. Baba, T. Kurahashi and S. Matsubara, *Org. Lett.* 2011, **13**, 1912; (e) Y. Yokoyama, Y. Unoh, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.* 2014, **79**, 7649; (f) K. Padala and M. Jeganmohan, *Chem. Commun.* 2014, **50**, 14573; (g) P. Villuendas and E. P. Urriolabeitia, *Org. Lett.* 2015, **17**, 3178; (h) A review: N. Kaur, *Catal. Rev.* 2015, **57**, 478.

9 The only alternative method we have found is the aryl-aryl coupling in haloaryl thioethers or sulfoxides, where only one C-C bond is formed: (a) T. Wesch, A. Berthelot-Bréhier, F. R. Leroux and F. Colobert, *Org. Lett.* 2013, **15**, 2490; (b) C. B. Bheeter, J. K. Bera and H. Doucet, *Adv. Synth. Catal.* 2012, **354**, 3533; (c) R. Samantha and A. P. Antonchick, *Angew. Chem. Int. Ed.* 2011, **50**, 5217; (d) B. Wang, Y. Liu, C. Lin, Y. Xu, Z. Liu and Y. Zhang, *Org. Lett.* 2014, **16**, 4574; (e) R. Che, Z. Wu, Z. Li, H. Xiang and X. Zhou, *Chem. Eur. J.* 2014, **20**, 7258.

10 (a) K. Tomooka, H. Yamamoto and T. Nakai, *Liebigs Ann./Recl.* 1997, 1275; (b) P. Bertolli, R. D. Farley, M. D. Fletcher, P. N. Horton, M. B. Hursthouse, C. Paradela and B. von Vacano, *Tetrahedron Lett.* 2006, **47**, 7939; (c) P. Antoniotti and G. Tonachini, *J. Org. Chem.* 1998, **63**, 9756; (d) K. Tomooka, H. Yamamoto and T. Nakai, *J. Am. Chem. Soc.* 1996, **118**, 3317.

11 The reaction of benzylthiolates with internal alkynes is mediated by Cu(OAc)$_2$ and gives tetrasubstituted olefins: P. Villuendas, S. Ruiz, P. Vidossich, A. Lledós and E. P. Urriolabeitia, *Chem. Eur. J.* 2018, **24**, 13124.

View Article Online
DOI: 10.1039/C8OB03201G

12 M. A. Bennett, T.-N. Huang, T. W. Matheson, A. K. Smith, S. Ittel and W. Nickerson, *Inorg. Synth.* 1982, **21**, 74.
13 CrysAlis RED, version 1.171.27p8; Oxford Diffraction Ltd., Oxford, U.K., 2005.
14 G. M. Sheldrick, SADABS, Program for absorption and other corrections, Göttingen University, 1996.
15 G. M. Sheldrick, SHELXS-86, *Acta Crystallogr. Sect. A* 1990, **46**, 467.
16 G. M. Sheldrick, SHELXL-97, *Acta Crystallogr. Sect. A* 2008, **64**, 112.