Catalytic [2+2+1] Synthesis of Fused Thiophenes Using Thiocarbonyls As Sulfur Donors

Kazuma Matsui,[a] Masatoshi Shibuya,[a] and Yoshihiko Yamamoto*[a]

Dedication ((optional))

Abstract: The use of *N*-(*p*-chlorophenyl)methylbenzoxazole-2-thione as a sulfur-atom donor enables the catalytic [2+2+1] cycloaddition of diynes in wet DMF at 80 °C in air, affording diverse fused thiophenes with good yields and wide functional group compatibility. A plausible mechanism, involving a cationic ruthenacycle intermediate was also proposed on the basis of several control experiments.

Thiophene is a privileged scaffold widely found in biologically active compounds and functional materials.[1] Although transition-metal-catalyzed approaches have been extensively developed to achieve diverse heterocycle syntheses under neutral conditions,[2] the catalytic synthesis of substituted thiophenes is underdeveloped because organosulfur compounds often inhibit the catalytic turnover by the strong coordination of the soft sulfur atom to the transition-metal catalysts.[3,4]

To establish a straightforward and versatile process, we focused on the transition-metal-mediated [2+2+1] approach, as it enables the construction of substituted thiophenes from readily available alkynes in a single operation. However, the requirement of stoichiometric amounts of preformed metallacycles, low efficiency, and/or limited scope remain to be addressed.[5] Although substituted thiophenes have been synthesized *via* zirconacyclopentadienes using S_2Cl_2 as the sulfur donor (Figure 1a),[6] the functional group compatibility is limited owing to the highly reducing character of 'Cp_2Zr'. Moreover, a metal-free [2+2+1] synthesis of thiophenes (Figure 1b)[7] and relevant methods using 1,3-diynes have been developed.[8] However, the substrate scope is still limited in previous methods.

We have previously reported transition-metal-catalyzed [2+2+1] cycloadditions of alkynes to afford substituted furans.[9] In these reports, catalytically generated ruthenacycle intermediates behaved as electrophilic biscarbenoids to undergo oxygen-atom transfer from DMSO or nitrones, allowing the catalytic formation of fused furans. Based on these results, we assumed that the yet elusive sulfur-atom transfer to similar ruthenacycle intermediates could be realized by judicious optimization of a sulfur donor and reaction conditions. Herein, we disclosed that a novel catalytic [2+2+1] cycloaddition of diynes involving a sulfur-atom transfer from thiocarbonyls to carbenoid carbons (Figure 1c). Notably, the newly developed process is robust and operationally simple, as the reaction can be performed in air and neither a dry solvent nor an inert atmosphere is necessary.

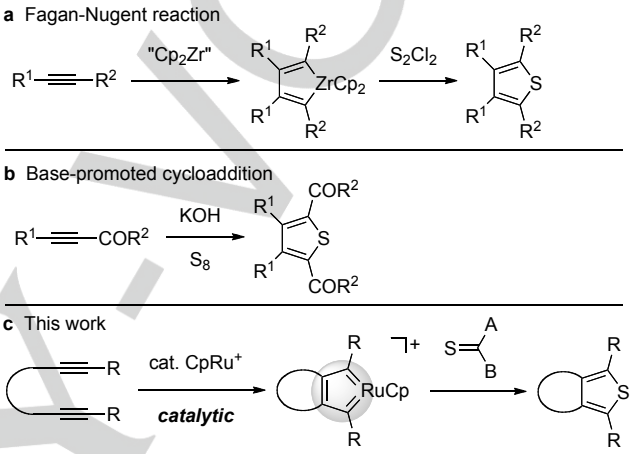
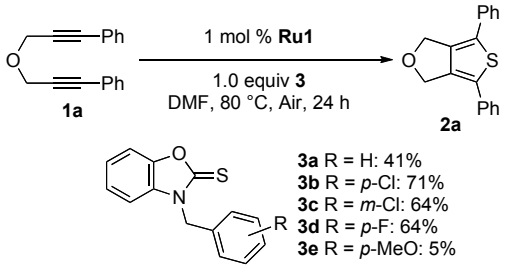


Figure 1. [2+2+1] Approaches to multisubstituted thiophenes.

The key to the successful realization of the elusive catalytic [2+2+1] synthesis of thiophenes is the identification of an optimal sulfur donor toward ruthenacycle intermediates as electrophilic biscarbenoids. To this end, conventional sulfur donors (Lawesson's reagent, thiirane, S_8, Na_2S, and $Na_2S_2O_3$) were screened. However, the expected product was not sufficiently obtained. Then, we evaluated thiocarbonyls as tunable sulfur donors, because a C=S bond has high polarizability owing to inefficient pπ–pπ overlap and, thus, is sufficiently nucleophilic. After extensive screening of thiocarbonyls (Figure S1 in Supporting Information), we found that benzoxazole-2-thione **3a** was a potent S donor (Scheme 1). Therefore, the *N*-benzyl moiety was further optimized by performing the reaction of diyne **1a** with 1 mol % $[CpRu(MeCN)_3]PF_6$ (**Ru1**, Cp = η^5-C_5H_5) at 80 °C using DMF in air. It was revealed that an electron-withdrawing group on the *N*-benzyl moiety has a favorable impact on the sulfur-atom transfer: *p*-chlorinated analog **8b** gave the best yield (71%), albeit with 21% of **1a** remained. *m*-Chloro and *p*-fluoro analogs **8c** and **8d** also produced **2a**, albeit in slightly lower yields, and **8e**, bearing an electron-donating methoxy group on the *N*-benzyl moiety, was in efficient. Notably, the reaction was sluggish in dry DMF and the yield of **2a** decreased to 35%, and unreacted **1a** and **3b** were recovered in 63% and 64% yields, respectively. This result implies that water plays an important role. Moreover, $[Cp^*Ru(MeCN)_3]PF_6$, bearing the bulky and electron-donating Cp* (η^5-C_5Me_5) ligand, proved to be a less efficient catalyst.

[a] K. Matsui, Dr. M. Shibuya, Prof. Dr. Y. Yamamoto
Department of Basic Medicinal Sciences
Graduate School of Pharmaceutical Sciences, Nagoya University
Chikusa, Nagoya 464-8601
E-mail: yamamoto-yoshi@ps.nagoya-u.ac.jp

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))



Scheme 1. Optimization of sulfur donor.

Using **3b** as the optimal sulfur donor, the general applicability of this method was investigated in terms of diyne substrates **1** (Figure 2). The reaction of **1a** was repeated with an increased catalyst loading (2 mol%) to observe complete conversion in 5 h, affording **2a** in 90% isolated yield. Similarly, other diynes **1b**–**j** were subjected to the reaction with 2–5 mol % catalyst loadings, affording the corresponding bicyclic thiophenes in 71–90% yields. Notably, various functional groups, including ester, ketone, amide, nitrile, sulfide, sulfone, and silyl ether, were well tolerated under the reaction conditions.

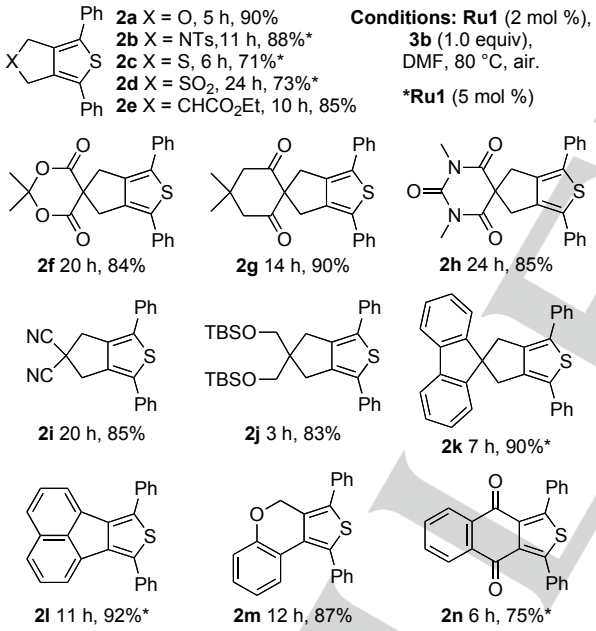


Figure 2. Scope of diyne substrates.

Spirocyclic fluorene derivative **2k** and acenaphtho[1,2-*c*]thiophene derivative **2l** were also synthesized in high yields. Moreover, this method proved to be applicable to six-membered ring formations, as 4*H*-thieno[3,4-*c*]chromene derivative **2m** and naphtho[2,3-*c*]thiophene-4,9-dione derivative **2n** were obtained in 87% and 75% yields, respectively. The latter compound was previously obtained in 62% yield from the stoichiometric reaction of a preformed rhodacyclopentadiene with elemental sulfur.[5a] The present protocol successfully improved the yield by using catalytic amounts of the less expensive ruthenium complex. The fused thiophene structure was unambiguously confirmed by single crystal X-ray analysis of **2k**.

Next, the influence of the terminal aryl groups of diyne substrates was investigated (Figure 3). The reactions of diynes **1o**–**r**, possessing electron-rich aryl terminals, proceeded with 2 mol % catalyst loadings, except for diyne **1p**, bearing sterically demanding *o*-substituted aryl terminals (10 mol %). The corresponding bicyclic thiophenes **2o**–**r** were obtained in high yields. In addition, diynes **1s**–**u**, bearing *p*-fluoro, *p*-iodo, and *p*-boryl groups on the aryl terminals, respectively, afforded the corresponding products in >90% yields, although 5 mol % catalyst loadings were required for **1s** and **1u**. In contrast, the reaction of diyne **1v**, possessing *p*-formylphenyl terminals, hardly produced the desired thiophene under the standard conditions with 2 mol % catalyst loadings.[10] This protocol enables the synthesis of such unsymmetrical push-pull thiophenes **2w**, **2x** and **2y** in high yields.[11] Moreover, tristhiophenes **2za**–**2zc** were synthesized in 67–92% yields. It is particularly significant that the reactive C–I, C–Br and C–B bonds, which can be utilized for further transformations, were preserved in the final products.

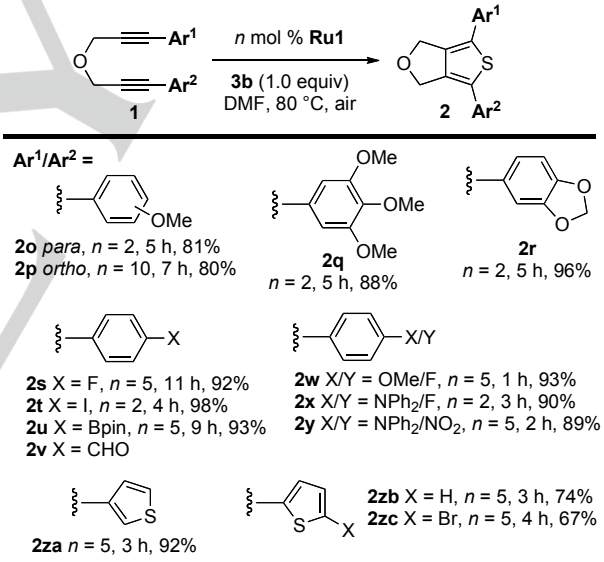
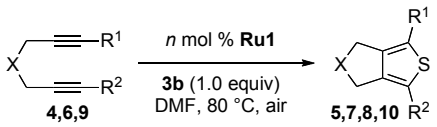


Figure 3. Influence of terminal aryl groups.

This method was also applicable to diyne substrates bearing alkyl or silyl terminal groups (Scheme 2). Diynes **4a** and **4b**, each bearing at least one alkyl terminal group afforded the corresponding bicyclic thiophenes **5a** and **5b**, albeit in moderate yields. In our previous study, silyldiynes could be converted into 2-silylfurans using nitrones as oxygen donors.[9b] In striking contrast, TMS groups were not tolerated under the present conditions: the reaction of diyne **6a**, bearing a TMS terminal group, afforded desilylated bicyclic thiophene **7** in 56% yield. Thus, diyne **6b** bearing a bulkier TBS terminal group was examined, affording the expected 2-silylthiophene **8** in 49% yield, along with **7** (36%). Taking advantage of the ready removability

of TMS groups, bis(silyl)diyne **9** was directly transformed into bicyclic thiophene **10**, which could not be obtained from the corresponding terminal diyne due to its facile [2+2+2] cyclodimerization. Finally, diphenylacetylene and (3-methoxyprop-1-ynyl)benzene were also subjected to the reaction conditions, affording only trace amounts of the expected thiophenes. Therefore, the catalytic [2+2+1] protocol is dependent on the intramolecular settings.



4a X = O, R^1 = Ph, R^2 = Me; *n* = 5, 3 h: **5a** 62%
4b X = O, R^1 = R^2 = Bu; *n* = 5, 21 h: **5b** 50%
6a X = O, R^1 = *p*-$MeOC_6H_4$, R^2 = TMS; *n* = 2, 2 h: **7** (R^2 = H); 62%
6b X = O, R^1 = *p*-$MeOC_6H_4$, R^2 = TBS; *n* = 2, 18 h: **8** 49% + **7** 36%
9 X = NTs, R^1 = R^2 = TMS; *n* = 2, 8 h: **10** (R^1 = R^2 = H); 53%

Scheme 2. Reactions of diynes bearing nonaromatic terminal groups.

To gain insights into the reaction mechanism, several control experiments were conducted. Previously reported ruthenacycle complex **11**[12] was allowed to react with sulphur donor **3b** upon treatment with $AgPF_6$ (1.1 equiv) in DMF at 80 °C for 1 h, affording thiophene **2a** in 54% yield (Figure 4). This result corroborates the involvement of cationic ruthenium biscarbene complexes in the present [2+2+1] cycloaddition. Moreover, careful inspection of the byproducts of the reaction of **1a** with **3b** led to the identification of formamide **12**, which was derived from **3b**. It was proposed that one H_2O molecule was involved in the transformation of **3b** to **12**. Thus, the reaction of **1a** and **3b** was repeated in the presence of D_2O (6 equiv) or $H_2{}^{18}O$ (6 equiv), with the other conditions being the same, affording **12**-d_1 and **12**-^{18}O, respectively. These results corroborate the involvement of a water molecule in the sulfur-atom transfer and are in good agreement with the fact that the reaction was sluggish in dry DMF. In the absence of H_2O, only trace amounts of **12** were detected and unidentifiable byproducts were also observed. In contrast, the reactions efficiently proceeded in wet DMF (H_2O < 0.1%) in air. These results imply that H_2O was not essential, but dramatically improved the reaction efficiency. Indeed, the reaction of **1a** with **3b** completed in only 2 h to afford **2a** in 91% yield when the reaction was carried out with 1.0 equiv H_2O in dry DMF (H_2O < 10 ppm) under Ar.

Based on these observations, a plausible mechanism was deduced as shown in Figure 4. The catalytic cycle starts with the oxidative cyclization of a diyne with the $CpRu^+$ fragment to generate cationic ruthenacycle **A** as a key intermediate. Subsequently, sulfur-atom transfer occurs from **3b** to the electrophilic carbene carbon of **A** to generate thiadienylcarbene complex **C**, which further undergoes cyclization to provide thiophene complex **D**. A similar cycloisomerization was proposed for the previous [2+2+1] furan formations.[9] The final ligand exchange from the resultant thiophene to a diyne restores ruthenacycle **A**, closing the catalytic cycle. Although the detail of the sulfur-atom-transfer step (**A** → **C**) is unclear at this stage, it is suggested that the attack of H_2O on the thiocarbonyl group of **3b**, which becomes electrophilic upon coordination (**B**), triggers the sulfur-atom transfer to the carbenoid carbon via transition state $\mathbf{TS_{BC}}$. An alternative route is the direct S transfer from the coordinated thiocarbonyl to the ruthenacycle with the concomitant formation of a free carbene, which reacted with H_2O to generate **12**.

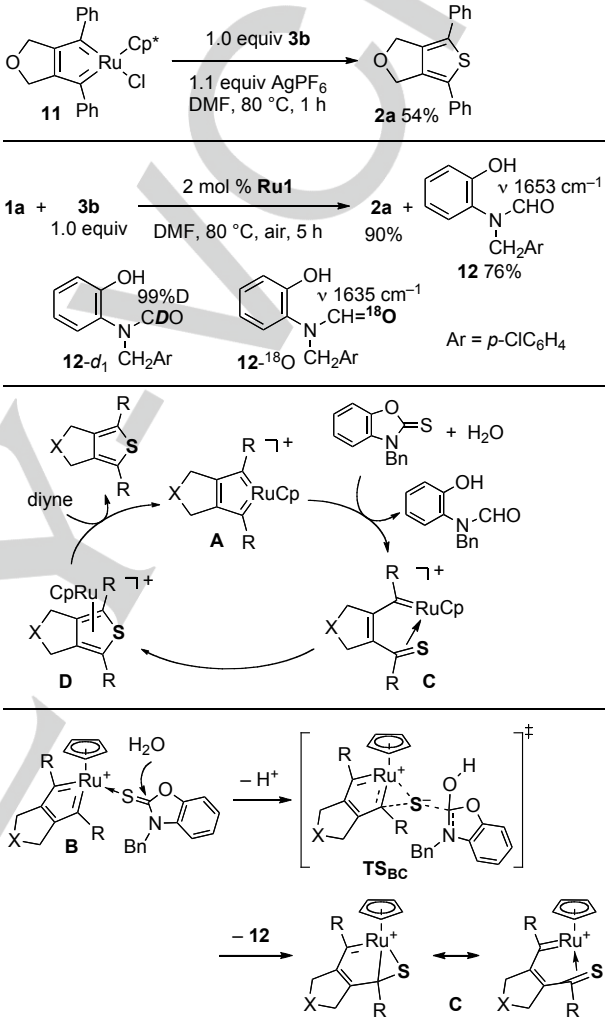


Figure 4. Control experiments and proposed mechanism.

In conclusion, we developed a catalytic [2+2+1] cycloaddition route to produce diverse fused thiophenes using *N*-(*p*-chlorophenyl)methylbenzoxazole-2-thione as the sulfur donor in wet DMF at 80 °C. The optimized protocol tolerated a wide variety of functional groups and enabled the reaction to proceed in air, obviating inert atmosphere and dry conditions. A plausible mechanism, involving a cationic ruthenacycle intermediate, for this catalytic process was also deduced from several control experiments. Interestingly, the sulfur-atom transfer from the thiocarbonyl group to the cationic carbenoid carbon possibly occurs with the attack of H_2O on the coordinated thiocarbonyl group.

Acknowledgements

This research is partially supported by AMED (Platform for Drug Discovery, Information, and Structural Life Science) and JSPS KAKENHI (Grand Number JP 16KT0051).

Keywords: Ruthenium • Alkyne • Thiocarbonyl • Cycloaddition • Thiophene

[1] a) G. Barbarella, M. Melucci, G. Sotgiu, *Adv. Mater.* **2005**, *17*, 1581-1593; b) S. C. Rasmussen, S. J. Evenson, C. B. McCausland, *Chem. Commun.* **2015**, *51*, 4528-4543; c) R. Mishra, K. K. Jha, S. Kumar, I. Tomer, *Der Pharma Chemica* **2011**, *3 (4)*, 38-54; d) D. Gramec, L. P. Mašič, M. S. Dolenc, *Chem. Res. Toxicol.* **2014**, *27*, 1344-1358.

[2] I. Nakamura, Y. Yamamoto *Chem. Rev.* **2004**, *104*, 2127-2198.

[3] T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205-3220.

[4] R. Mancuso, B. Gabriele, *Molecules* **2014**, *19*, 15687-15719.

[5] a) E. Müller, *Synthesis* **1974**, 761-774; b) Y. Wakatsuki, T. Kuramitsu, H. Yamazaki, *Tetrahedron Lett.* **1974**, 4549-4552; c) M. Kajitani, T. Suetsugu, R. Wakabayashi, A. Igarashi, T. Akiyama, A. Sugimori, *J. Organomet. Chem.* **1985**, *293*, C15-C18.

[6] a) X. Yan, C. Xi, *Acc. Chem. Res.* **2015**, *48*, 935-946. Also, see: b) W. You, X. Yan, Q. Liao, C. Xi, *Org. Lett.* **2010**, *12*, 3930-3933.

[7] W. Liu, C. Chen, H. Liu, *Adv. Synth. Catal.* **2015**, *357*, 4050-4054.

[8] a) M. L. N. Rao, S. S. Islam, P. Dasgupta, *RSC Adv.* **2015**, *5*, 78090-78098; b) I. Talbi, C. Alayrac, J.-F. Lohier, S. Touil, B. Witulski, *Org. Lett.* **2016**, *18*, 2656-2659.

[9] a) K. Yamashita, Y. Yamamoto, H. Nishiyama, *J. Am. Chem. Soc.* **2012**, *134*, 7660-7663; b) K. Matsui, M. Shibuya, Y. Yamamoto, *ACS Catal.* **2015**, *5*, 6468-6472.

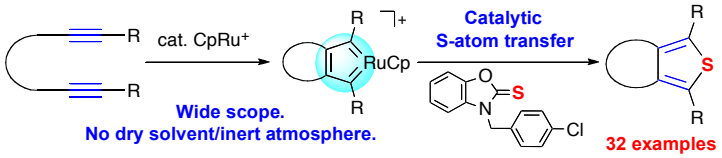
[10] The inefficiency of **1v** can be ascribed to the electron-withdrawing effect of the terminal groups. The reaction of **1a** with **8b** was conducted in the presence of 2 equiv of benzaldehyde under the standard conditions, affording **2a** in 83% yield. This result indicates that the formyl group is tolerated under the reaction conditions.

[11] Thiophene derivatives substituted by electron-donors and electron-acceptors at the 2- and 5-positions, respectively, have received much attention as push–pull chromophores for organic solar cells (V. Malytskyi, J.-J. Simon, L. Patrone, J.-M. Raimundo, *RSC Adv.* **2015**, *5*, 354-397). Indeed, **2x** showed a blue photoluminescence in both a solid state and a solution when irradiated by a UV lamp (365 nm). Fluorescence spectra of **2x** and **2y** with λ_{max} at 464 and 430 nm, respectively, were obtained when excited at 398 nm in CH_2Cl_2 (Fig. S4 in Supporting Information).

[12] Y. Yamamoto, T. Arakawa, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2003**, *125*, 12143-12160.

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



*K. Matsui, M. Shibuya, Y. Yamamoto**

Page No. – Page No.

Catalytic [2+2+1] Synthesis of Fused Thiophenes Using Thiocarbonyls As Sulfur Donors

The use of *N*-(*p*-chlorophenyl)methylbenzoxazole-2-thione as a sulfur-atom donor enables the catalytic [2+2+1] cycloaddition of diynes in wet DMF at 80 °C in air, affording diverse fused thiophenes with good yields and wide functional group compatibility. A plausible mechanism, involving a cationic ruthenacycle intermediate was also proposed on the basis of several control experiments.