PAPER

Palladium-catalyzed bisthiolation of terminal alkynes for the assembly of diverse (Z)-1,2-bis(arylthio)alkene derivatives†

Yin-Long Lai,*[a] Shaoxi Yan,‡[a] Dan He,‡[b] Li-Zhen Zhou,[a] Zi-Shen Chen,[a] Yu-Long Du[a] and Jianxiao Li [ID] *[bc]

An efficient and straightforward palladium-catalyzed three-component cascade bisthiolation of terminal alkynes and arylhydrazines with sodium thiosulfate ($Na_2S_2O_3$) as the sulfur source for the assembly of functionalized (Z)-1,2-bis(arylthio)alkene derivatives is described. Using 0.5 mol% IPr−Pd−Im−Cl_2 as the catalyst, a wide range of terminal alkynes and arylhydrazines are well tolerated, thus producing the desired products in good yields with good functional group tolerance and excellent regioselectivity. Moreover, this protocol could be readily scaled up, showing potential applications in organic synthesis and material science.

Introduction

Transition-metal-catalyzed functionalization of unsaturated hydrocarbons (such as alkenes and alkynes) is proven to be a flexible and straightforward synthetic strategy for the assembly of structurally diverse organic synthetic building blocks in organic synthesis, advanced materials, and pharmaceutical chemistry.[1] Among them, the functionalization reaction of alkynes has witnessed considerable attention in recent years because of their idiographic nucleophilic and electrophilic properties.[2] In this regard, transition-metal-catalyzed difunctionalization of alkynes has become one of the most powerful synthetic methodologies for the effective synthesis of diverse complex polysubstituted olefins from abundant and readily available starting materials in an atom- and step-economical manner.[3] Nevertheless, this protocol required two elements of the *p*-block (RE–ER, E = B, S, Si, C…) as the coupling partners. In terms of green chemistry, the photo-catalyzed difunctionalization of alkynes has also attracted more attention in recent years.[4] Apart from the above synthetic methods, metal-free radical addition reaction of alkynes with radical precursors has triggered a multiplication of synthetic protocols for accessing a vast array of value-added

functionalized molecules.[5] However, the scope of the free radical is limited to the common free radical precursors. Therefore, it is highly desirable to develop a novel and efficient synthetic approach for the straightforward difunctionalization of alkynes from readily available starting materials under eco-friendly conditions.

In addition, organosulfur structural frameworks are prevalent in organic synthesis, natural products, and various bioactive molecules.[6] In particular, among a whole variety of vinyl sulfide scaffolds, the 1,2-bis(arylthio)alkene derivatives exhibit remarkable biological activities and pharmaceuticals activities.[7] As a result, a library of representative synthetic methodologies have been developed for the preparation of this vinyl sulfide scaffolds. Undoubtedly, transition-metal-catalyzed bisthiolation of terminal alkynes with diaryl disulfides have been identified as the extremely rapid and efficient synthetic strategy for constructing these motifs (Scheme 1a). And, several noble metal catalysts such as Pd,[8] Rh,[9] Ni[10] have displayed a remarkable catalytic activity for this chemical transformation. For instance, Ananikov and co-workers developed a nice palladium-catalyzed addition reaction of disulfides with alkynes under solvent free conditions for the synthesis of structurally diverse (Z)-1,2-bis(arylthio)alkenes in good yields. Yamaguchi and co-workers also disclosed a rhodium-catalyzed addition reaction of dialkyl disulfides with terminal alkynes for the construction of various (Z)-bis(alkylthio)olefins with excellent stereoselectively. Additionally, in 2009, Xu and Yang and co-workers reported a cesium hydroxide catalyzed addition reaction of diaryl disulfides with terminal alkynes for constructing a series of (Z)-1,2-bis(arylthio) alkene derivatives (Scheme 1b).[11] However, these reactions needed diaryl disulfides and dialkyl disulfides as the sulfenylating reagents. In 2018, our group have also successfully developed an NHC-palladium-catalyzed three-component

[a]*College of Chemistry and Civil Engineering, Shaoguan University, Shaoguan, 512005, P. R. China. E-mail: chemlaiyinlong@163.com*
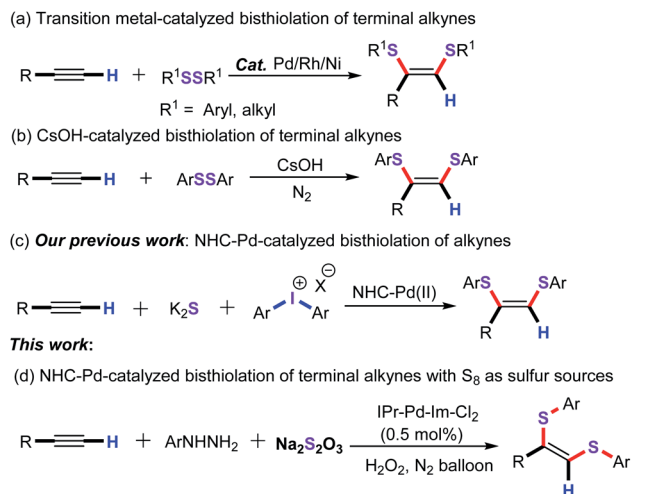
[b]*Key Laboratory of Functional Molecular Engineering of Guangdong Province, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China. E-mail: cejxli@scut.edu.cn*

[c]*Guangdong Provincial Key Laboratory of Luminescence from Molecular Aggregates, South China University of Technology, Guangzhou 510640, China*

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‡ These two authors contributed equally.

(a) Transition metal-catalyzed bisthiolation of terminal alkynes

(b) CsOH-catalyzed bisthiolation of terminal alkynes

(c) *Our previous work*: NHC-Pd-catalyzed bisthiolation of alkynes

This work:

(d) NHC-Pd-catalyzed bisthiolation of terminal alkynes with S_8 as sulfur sources

**Scheme 1** Representative strategies for the synthesis of (Z)-1,2-bis(arylthio)alkenes.

cascade bisthiolation of terminal alkynes, K_2S and diaryliodonium salts for the assembly of functionalized (Z)-1,2-bis(arylthio)alkenes derivatives with high regioselectivity (Scheme 1c).[12] Despite the significance, the alternative sulfenylating reagents such as sodium thiosulfate ($Na_2S_2O_3$) have rarely reported in this chemical transformation.[13] To the best of our knowledge, there is no synthetic example for the synthesis of (Z)-1,2-bis(arylthio)alkenes with $Na_2S_2O_3$ as the sulfenylating reagent. Inspired by our longstanding interest in Pd-catalyzed coupling reactions of alkynes,[14] and organosulfur chemistry,[15] we herein describe a novel palladium-catalyzed three-component cascade bisthiolation of terminal alkynes and arylhydrazines with $Na_2S_2O_3$ as the sulfur source for the assembly of functionalized (Z)-1,2-bis(arylthio)alkene derivatives in good to excellent yields (Scheme 1d).

Results and discussion

As an initial experiment, ethynylbenzene (**1a**), phenylhydrazine hydrochloride (**2a**), and sodium thiosulfate ($Na_2S_2O_3$) was employed as the model substrates to screen for the optimal reaction conditions, and the representative results are summarized in Table 1. Preliminary screening revealed that IPr–Pd–Im–Cl$_2$ as the catalyst was the most effective palladium catalysts for this protocol, while other catalysts such as PdCl$_2$, Pd(TFA)$_2$, Pd(PhCN)$_2$Cl$_2$, [Pd(allyl)Cl]$_2$, Pd(PPh$_3$)$_2$Cl$_2$, IPr–Pd–allyl–Cl, and IPr–Pd–Cin–Cl showed low efficiencies (entries 1–8). Among the oxidants tested, 35% H$_2$O$_2$ gave the best results (entries 10–12). Subsequently, different bases were examined, including Et$_3$N, DBU, CsF, and Cs$_2$CO$_3$, the results showed that Cs$_2$CO$_3$ was the most effective base for this transformation (entries 7 and 13–15). Further exploration of the solvent indicated that DMSO was superior to the DMF and toluene (entries 7, 16 and 17). Inspired by our previous studies, we found that ionic liquids as the solvent showed apparent positive effects in palladium-catalyzed coupling reaction.[16] Thus, we also estimated the ionic liquids as the green solvent for this

Table 1 Optimization of reaction conditions[a]

Entry	Catalyst	Oxidant	Base	Solvent	Yield[b] (%)
1	PdCl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	0
2	Pd(TFA)$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	Trace
3	Pd(PhCN)$_2$Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	13
4	[Pd(allyl)Cl]$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	22
5	Pd(PPh$_3$)$_2$Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	Trace
6	IPr–Pd–allyl–Cl	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	37
7	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	54
8	IPr–Pd–Cin–Cl	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	41
9	(IPr–Pd–Cl$_2$)$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMF	38
10	IPr–Pd–Im–Cl$_2$	O$_2$	Cs$_2$CO$_3$	DMF	Trace
11	IPr–Pd–Im–Cl$_2$	NFSI	Cs$_2$CO$_3$	DMF	33
12	IPr–Pd–Im–Cl$_2$	PhI(OAc)$_2$	Cs$_2$CO$_3$	DMF	46
13	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Et$_3$N	DMF	26
14	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	DBU	DMF	Trace
15	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	CsF	DMF	18
16	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	DMSO	56
17	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	Toluene	Trace
18	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	[Bmim]Cl	72
19	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	[Bmim]BF$_4$	65
20	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	[Bmim]PF$_6$	90 (84)
21	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	PEG-200	Trace
22	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	PEG-400	Trace
23	—	H$_2$O$_2$	Cs$_2$CO$_3$	[Bmim]PF$_6$	0
24[c]	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	[Bmim]PF$_6$	90
25[d]	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	[Bmim]PF$_6$	90
26[e]	IPr–Pd–Im–Cl$_2$	H$_2$O$_2$	Cs$_2$CO$_3$	[Bmim]PF$_6$	78

IPr-Pd-Allyl-Cl   **IPr-Pd-Im-Cl$_2$**   **IPr-Pd-Cin-Cl**   **(IPr-Pd-Cl$_2$)$_2$**
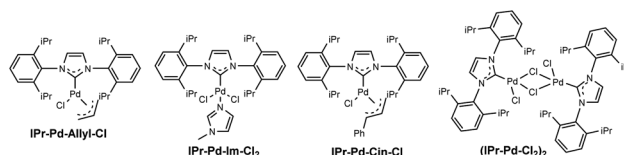
[a] Reactions were performed with **1a** (0.10 mmol), **2a** (0.24 mmol), Na$_2$S$_2$O$_3$ (0.20 mmol), catalyst (3 mol%), oxidant (0.20 mmol), base (0.20 mmol), solvent (1 mL) at 120 °C under N$_2$ for 12 h. [Bmim]Cl: 1-butyl-3-methylimidazolium chloride. [Bmim]BF$_4$: 1-butyl-3-methylimidazolium tetrafluoroborate. [Bmim]PF$_6$: 1-butyl-3-methylimidazolium hexafluorophosphate. PEG-200: polyethylene glycol 200. PEG-400: polyethylene glycol 400. [b] Determined by GC using dodecane as the internal standard. The value in parentheses is the yield of isolated product. [c] 1 mol% IPr–Pd–Im–Cl$_2$ was used. [d] 0.5 mol% IPr–Pd–Im–Cl$_2$ was used. [e] At 110 °C.

transformation. It is noteworthy that ionic liquid [Bmim]PF$_6$ as the solvent was found to be the best choice, and the desired product **3a** was afforded in 90% GC yield (entry 20). In addition, the green PEG-200 and PEG-400 were also screened, however, only a trace amount of the desired product **3a** was detected by GC-MS (entries 21 and 22). It is particularly noteworthy that the desired product **3a** was still obtained in 90% GC yield when the reaction was performed with 0.05 mol% dosage of the IPr–Pd–Im–Cl$_2$ catalyst (entry 25). Finally, the yield of **3a** decreased dramatically when the temperature was used at 110 °C under the similar condition (entry 26).

Under the optimized conditions, the substrate scope of various alkynes was then explored, and the results are presented in Table 2. In general, both aryl alkynes and alkyl alkynes can react with phenylhydrazine hydrochloride (**2a**), and sodium thiosulfate ($Na_2S_2O_3$) in the optimized conditions, producing the desired products **3** in good to excellent yields with good regioselectivity. As anticipated, the aryl alkynes bearing alkyl, alkoxyl, fluoro, chloro, amino, acetyl, and cyano group on the phenyl ring were perfectly accommodated in the optimized conditions to deliver the desired products **3a–3h** with yields in the range of 70–92%. Specifically, this approach was compatible with the halogen atom substituent on the aryl ring such as –Cl, which might allow for further functional group derivatization by transition metal-catalyzed chemical transformation. In addition, the electronic properties of the substituents such as electron-donating group ($–NMe_2$) and electron-withdrawing group (–Ac, CN) on the benzene ring of aryl alkynes did not have a significant influence on the reaction efficiency. Moreover, 1-ethynylnaphthalene (**1i**) was tolerated well, giving the corresponding product **3i** in 86% yield. To our delight, 2-ethynylthiophene (**1j**) and 4-ethynylpyridine (**1k**) were also perfectly tolerated, furnishing the desired **3j** and **3k** in 73% and 65% yields, respectively. As for the alkyl alkynes, both the linear chain alkynes and the cyclo-alkynes were all nicely tolerated, and gave the desired products in good to excellent yields. Gratifyingly, the substrate containing vinyl group also performed well under the optimized conditions, and generated the corresponding product **3p** in 91% yield. Additionally, the substrates containing free hydroxyl of linear chain alkynes also worked well, delivering the corresponding products **3q** and **3s** in 72% and 83% yields, respectively. Notably, ethynyl-trimethylsilane (**1r**) was nicely compatible with the current catalytic system and afforded the corresponding **3r** in 76% yield. Unfortunately, the internal alkynes such as 1,2-diphenylethyne, and pent-2-yne were not tolerated with the current system. The probable reason is that the steric hindrance of internal alkynes hindered the nucleopalladation process.[17]

Encouraged by the above positive results, we then evaluated the limitation and compatibility of various arylhydrazines in the optimized conditions. As illustrated in Table 3, both electron-neutral substituents (Me, *t*Bu) and electron-withdrawing groups (F, Cl, Br, Ac) on the benzene ring were nicely tolerated and gave the expected products **4a–4f** in good to high yields. It is remarkable that the substrate thiophen-3-ylhydrazine could also react smoothly to deliver the desired product **4g** in 66% yield.

Subsequently, to further probe to the possible sulfur intermediate in this catalytic system, several easily available sulfur sources were investigated under the optimized conditions. As shown in Scheme 2, the S_8 and Na_2S were not the alternative sulfenylating reagents, and failed to furnish the desired product **3a**. Amazingly, when PhSH was employed as the sulfenylating agents, the desired product **3a** was detected in 57% GC yield. This observation demonstrated that PhSH might be the possible intermediate in this bisthiolation reaction. In contrast, when PhSSPh was used as the sulfenylating agent, no the desired product **3a** was observed by GC-MS analysis.

Next, various aryl reagents were explored as well to examine the substrate applicability of this synthetic strategy (Scheme 3). For instance, the cascade denitrogenative/bisthiolation of phenyldiazonium salt (**5a**) with ethynylbenzene (**1a**) allowed successfully to give the product **3a** in 69% yield (Scheme 3a). Unfortunately, the desulfitative/bisthiolation of sodium

Table 2 Substrate scope of various alkynes[a]

Table 3 Substrate scope of various arylhydrazines[a]
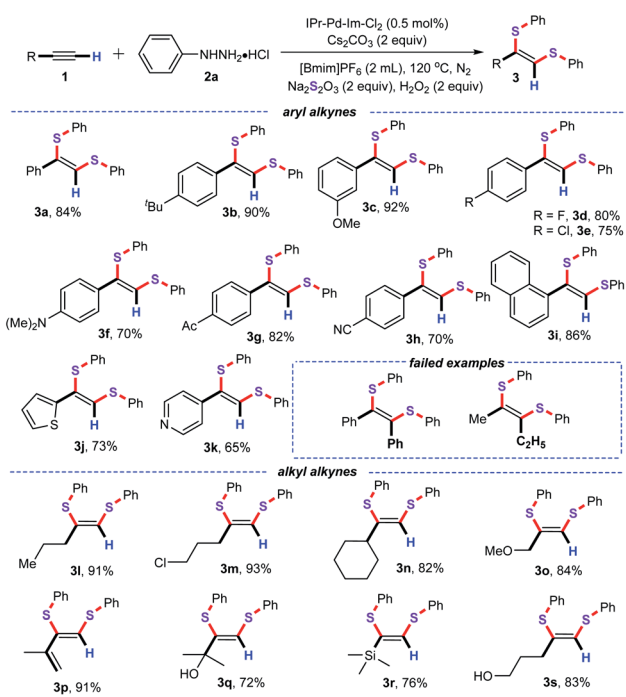
[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.48 mmol), $Na_2S_2O_3$ (0.40 mmol), IPr–Pd–Im–Cl_2 (0.5 mol%), H_2O_2 (0.4 mmol), Cs_2CO_3 (0.4 mmol), [Bmim]PF_6 (2 mL) at 120 °C for 12 h. Yields referred to isolated yield.
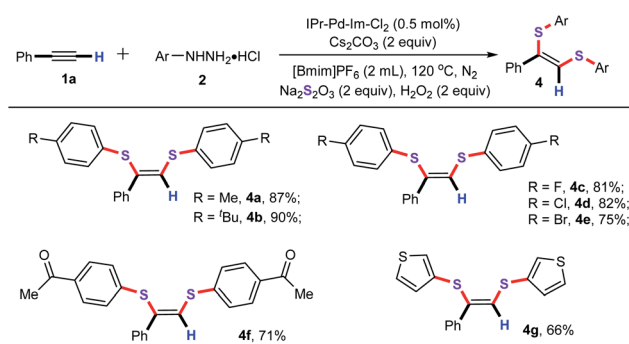
[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.48 mmol), $Na_2S_2O_3$ (0.40 mmol), IPr–Pd–Im–Cl_2 (0.5 mol%), H_2O_2 (0.4 mmol), Cs_2CO_3 (0.4 mmol), [Bmim]PF_6 (2 mL) at 120 °C for 12 h. Yields referred to isolated yield.
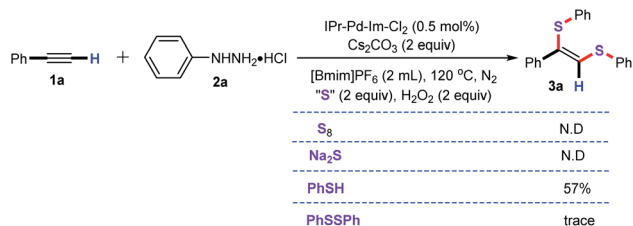
**Scheme 2** Investigation of different sulfur sources.
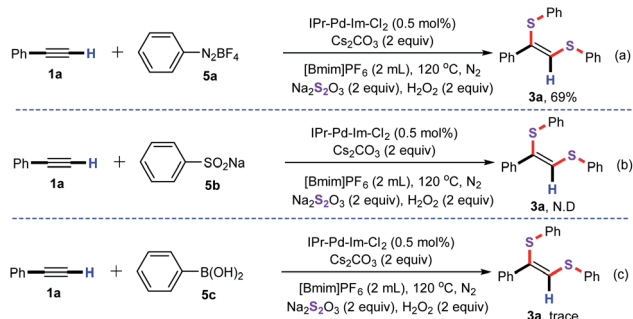
**Scheme 3** Investigation of different arylation reagents.

benzenesulfinate (**5b**) with ethynylbenzene (**1a**) cannot carry out under the optimized conditions, and no the desired product **3a** was observed by GC-MS (Scheme 3b). Similarly, the cascade Suzuki/bisthiolation of phenylboric acid (**5c**) with **1a** also tested under the standard conditions, however, only a trace amount of the desired product **3a** was detected by GC-MS (Scheme 3c).

Delightfully, this approach was successfully scaled up to 4 mmol, and the desired product **3a** was obtained in 81% yield (Scheme 4).

Based on these experimental results and previous literature precedents, a plausible mechanism for this cascade bisthiolation process is proposed in Scheme 5. Initially, in the presence of base, the arylhydrazine reacts with Pd(II) to give the aryl palladium species by releasing the N_2. Then, ligand exchange between the aryl palladium species and $Na_2S_2O_3$ to form palladium thiosulfate intermediate, which can generate the sodium thiophenolate **I** *via* the release of SO_3.[18] Nucleopalladation of sodium thiophenolate **I** with alkynes gives vinyl palladium intermediate **II**. Subsequently, the anion exchange process from intermediate **II** with ArSNa to produce the intermediate **III**. Finally, the reductive elimination process generates the desired products and the Pd[0] active species. In light of our previously observed results, we found that ionic liquids as the solvent or cosolvent system showed apparent positive effects for the formation of the thiophenolate anion.[15,19,20]
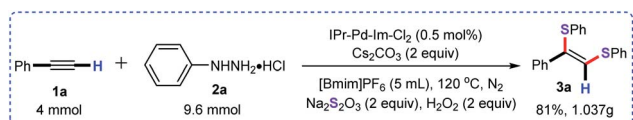
Scheme 4 Gram-scale reaction.
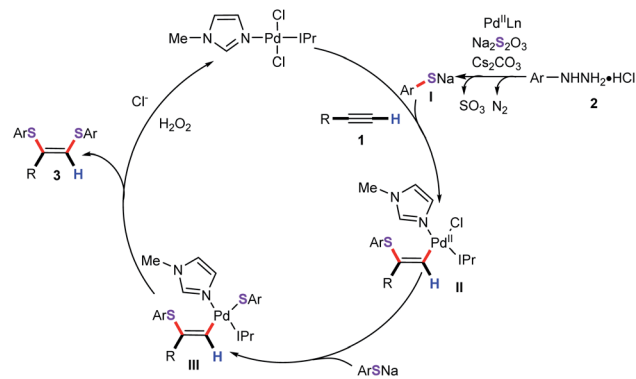
Scheme 5 Possible mechanism.

Conclusions

In conclusion, we have established a novel and efficient palladium-catalyzed three-component cascade bisthiolation of terminal alkynes and arylhydrazines with $Na_2S_2O_3$ as the sulfur source for the assembly of functionalized (Z)-1,2-bis(arylthio) alkene derivatives in good to excellent yields with high regioselectivity. This protocol features mild conditions, excellent regioselectivity and good functional group tolerance. Prominently, H_2O_2 as the green oxidant and IPr–Pd–Im–Cl$_2$ as the catalyst play an essential role in this protocol. Notably, in the presence of 0.5 mol% of IPr–Pd–Im–Cl$_2$ as the catalyst, a wide range of alkynes and various arylhydrazines are excellently tolerated. Preliminary mechanistic studies suggest that the sodium thiophenolate might be involved in this transformation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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