Coupling Reagents

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Enabling the Use of Alkyl Thianthrenium Salts in Cross-Coupling Reactions by Copper Catalysis

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Abstract: *Alkyl groups are one of the most widely used groups in organic synthesis. Here, a a series of thianthrenium salts have been synthesized that act as reliable alkylation reagents and readily engage in copper-catalyzed Sonogashira reactions to build C(sp^3)–C(sp) bonds under mild photochemical conditions. Diverse alkyl thianthrenium salts, including methyl and disubstituted thianthrenium salts, are employed with great functional breadth, since sensitive Cl, Br, and I atoms, which are poorly tolerated in conventional approaches, are compatible. The generality of the developed alkyl reagents has also been demonstrated in copper-catalyzed Kumada reactions.*

Sulfonium salts bearing sulfur ions and three organic functional groups have intrigued chemists for more than a century because of their high chemical reactivity.[1] In this regard, these compounds resemble organic halides with their excellent nucleofugal properties, easy single-electron reduction, and oxidative addition to transition metals.[2] The resulting S-(aryl/alkyl) sulfonium salts have been widely applied as aryl reagents in reactions because of the favorable energetics of the C(sp^2)–S bond cleavage (Figure 1a).[3] Moreover, they can also facilely form sulfur ylides by α-deprotonation.[4] Thus, the generation of alkyl species from sulfonium salts in cross-coupling reactions through C(sp^3)–S bond cleavage is synthetically challenging. Of the sulfonium salts, thianthrenium salts have recently attracted considerable attention from chemists.[5] Ritter and co-workers uncovered the immense synthetic value of aryl thianthrenium salts, produced by functionalization of C(aryl)–H bonds, in a wide range of reactions (Figure 1b).[6] These results inspired us to investigate whether thianthrenium salts might undergo cross-coupling reactions through selective C(sp^3)–S bond cleavage to provide alkyl species, thereby addressing some key shortcomings of conventional sulfonium salts.

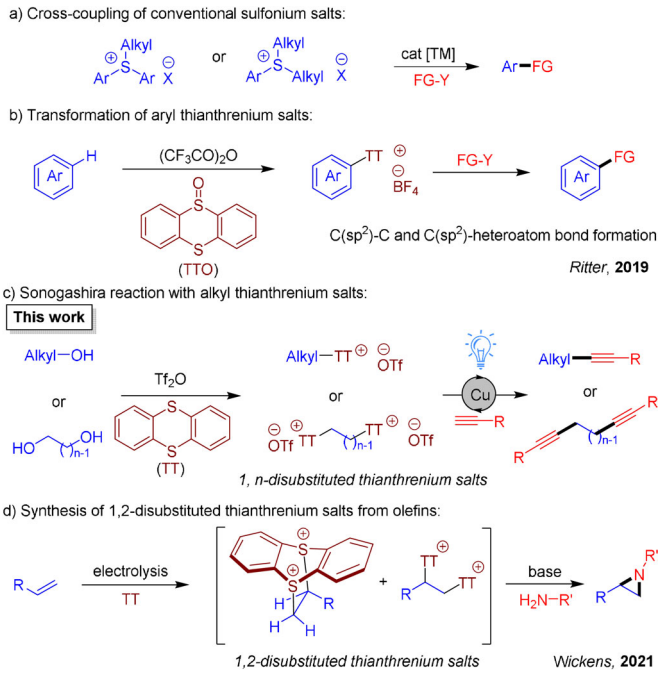

Figure 1. Employment of alkyl thianthrenium salts in Sonogashira reactions.

The Sonogashira reaction has been one of the most widely used strategies for the synthesis of high-value internal alkynes from organic halides and terminal alkynes.[7] As a proof of concept, we report here that a broad range of alkyl thianthrenium salts can be used in the Sonogashira reaction to build C(sp^3)–C(sp) bonds in the presence of copper catalysts under irradiation with blue LEDs (Figure 1c).[8] Other types of cross-coupling reactions, such as the Kumada reaction,[9] were also performed to form C(sp^3)–C(sp^3) and C(sp^3)–C(sp^2) bonds by copper catalysts and showed the excellent generality of these alkyl reagents. In our study, alkyl thianthrenium salts were conveniently produced from alcohols by adding thianthrene (TT) and Tf_2O reagents.[10] Notably, the Wickens group recently reported the electrochemical synthesis of 1,2-disubstituted thianthrenium salts from alkenes and TT. These salts act as the key intermediates in the production of aziridines (Figure 1d).[11] Using our method, 1,*n*-disubstituted thianthrenium salts can also be generated from the related diols and allow the facile construction of valuable diynes.

An extensive screening of conditions was performed using thianthrenium salt **1a** and alkyne **2a** as model substrates

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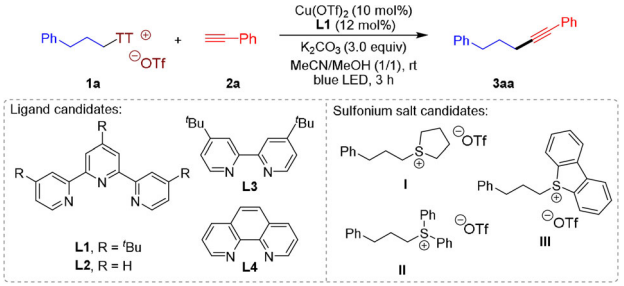
Table 1: Reaction optimization.[a]



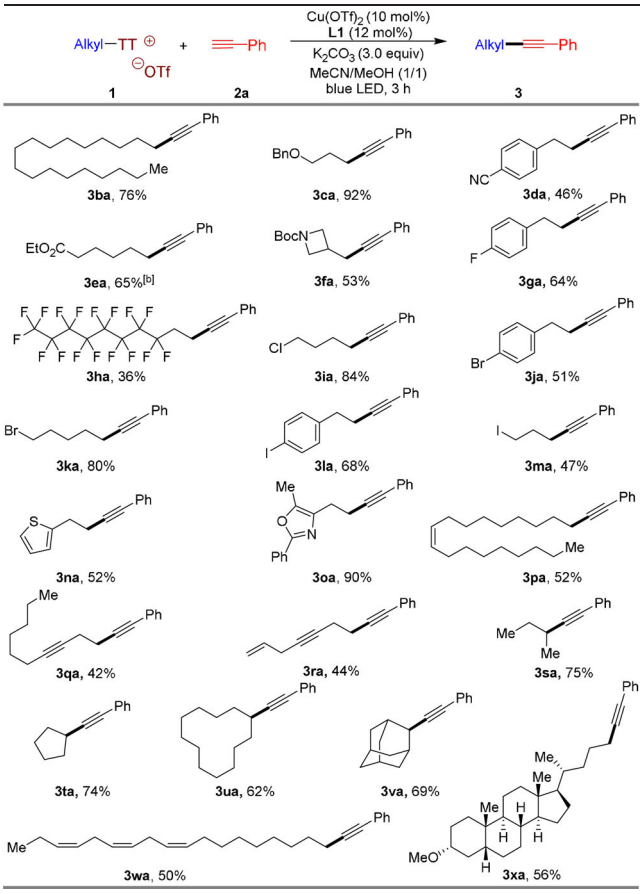
Entry	Variation from the standard conditions	Yield of **3aa** [%][b]
1	none	95 (85)[c]
2	using **L2** instead of **L1**	89
3	using **L3** instead of **L1**	52
4	using **L4** instead of **L1**	18
5	using **I** instead of **1a**	trace
6	using **II** instead of **1a**	26
7	using **III** instead of **1a**	65
8	without **L1**	26
9	in the dark	0
10	without $Cu(OTf)_2$	0

[a] Standard conditions: $Cu(OTf)_2$ (10 mol%), **L** (12 mol%), alkyl sulfonium salts **1a/I–III** (0.20 mmol), **2a** (0.24 mmol), K_2CO_3 (0.6 mmol), CH_3CN/MeOH (0.5 mL/0.5 mL), at room temperature, blue LED, under N_2, 3 h. [b] The yields were determined by ^1H NMR spectroscopic analysis of the crude product using CH_2Br_2 as a standard. [c] Yield of isolated **3aa**.

(Table 1). A catalytic amount of $Cu(OTf)_2$ (10 mol%), terpyridine **L1** (12 mol%), K_2CO_3 (3.0 equiv) as a base, and MeCN and MeOH as a cosolvent were reacted at room temperature under blue-LED irradiation for 3 h, which afforded the desired alkynylation product **3aa** in 95% yield (entry 1). Other ligands were also screened: terpyridine **L2** gave a slightly lower yield (entry 2), while bidentate ligands such as **L3** and **L4** exhibited much lower reactivity (entries 3 and 4). Other types of sulfonium salts were screened as well. Tetrahydrothiophene-derived sulfonium salt **I** exhibited a very low reactivity (entry 5). As expected, the reaction of diphenyl sulfonium salt **II** with **2a** only generated the desired product **3aa** in 26% yield, along with 1,2-diphenylethyne (65% yield) as the major product, which indicates that the C(sp^2)–S bond cleavage occurs preferentially over the C(sp^3)–S bond cleavage (entry 6). In addition, a dibenzothiophenium salt **III**[12] also showed excellent chemoselectivity for the C(sp^3)–S cleavage and provided the desired product **3aa** in a moderate yield (entry 7). Control experiments demonstrated that a diminished yield was observed without the ligand (entry 8), and both irradiation with visible light and a copper catalyst were essential for the reaction (entries 9 and 10).

Using the optimized reaction conditions, we first tested the scope of the alkyl thianthrenium salts in this cross-coupling with alkyne **2a** (Table 2). A range of primary alkyl thianthrenium salts was efficiently transformed into the corresponding products, including those with ether (**1c**), cyano (**1d**), ester (**1e**), and azetidine (**1f**) motifs. Compared to the traditional Sonogashira reaction using organohalides,[13] the unique chemoselectivity of this reaction was

Table 2: Substrate scope of alkyl thianthrenium salts.[a]

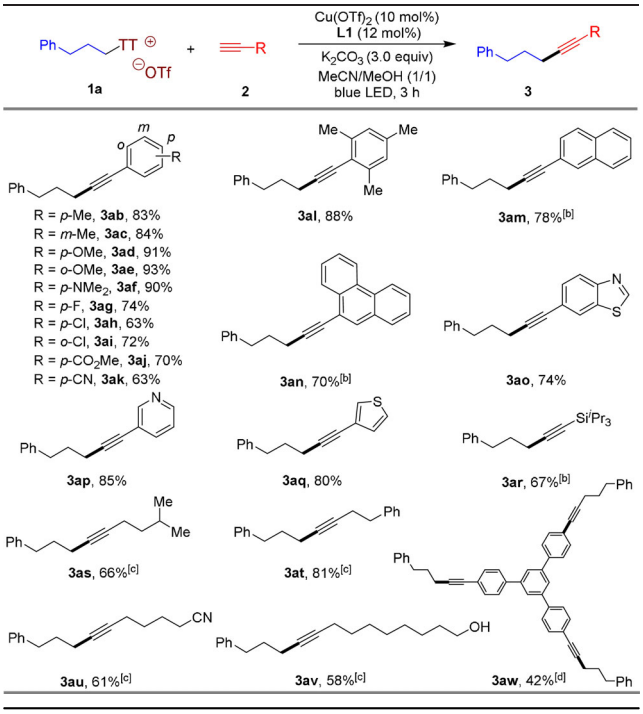


[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), **L1** (12 mol%), **1** (0.20 mmol), **2a** (0.24 mmol), K_2CO_3 (0.60 mmol), CH_3CN/MeOH (0.5 mL/0.5 mL), at room temperature, blue LED, under N_2, 3 h; yields are of isolated products. [b] CH_3CN/EtOH (0.5 mL/0.5 mL).

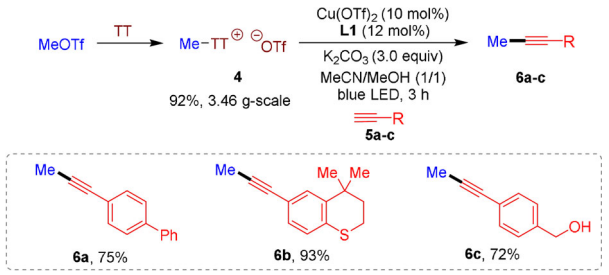
nicely showcased by the perfect accommodation of substrates with both alkyl and aryl halides, including F (**1g**, **1h**), Cl (**1i**), Br (**1j**, **1k**), and even I (**1l**, **1m**). This method was applicable to thianthrenium salts bearing heteroaryl motifs, such as thiophene (**1n**) and oxazole (**1o**). The transformations of thianthrenium salts bearing alkenyl and alkynyl groups (**1p**–**1r**) led to the formation of several useful enynes that are extremely laborious to access. In addition, secondary alkyl thianthrenium salts with both acyclic (**1s**) and cyclic (**1t**–**1v**) motifs worked very well. Compound **1w**, which was derived from α-linolenic acid with three *cis* double bonds, could convert into product **3wa** in modest yield with complete retention of the *Z*-configuration. Finally, a complex thianthrenium salt **1x** prepared from lithocholic acid also displayed good reactivity.

The substrate scope of the terminal alkynes was then examined with alkyl thianthrenium salt **1a** (Table 3). A wide range of arylacetylenes with Me (**2b**, **2c**), OMe (**2d**, **2e**), NMe_2 (**2f**), F (**2g**), Cl (**2h**,**i**), CO_2Me (**2j**), and CN (**2k**) groups at each position of the aryl motif were readily tolerated. Alkynes bearing mesitylene (**2l**), naphthalene (**2m**), and phenanthrene (**2n**) could couple with **1a** with good efficiency. Heteroarene-substituted alkynes, including benzo[*d*]thiazole

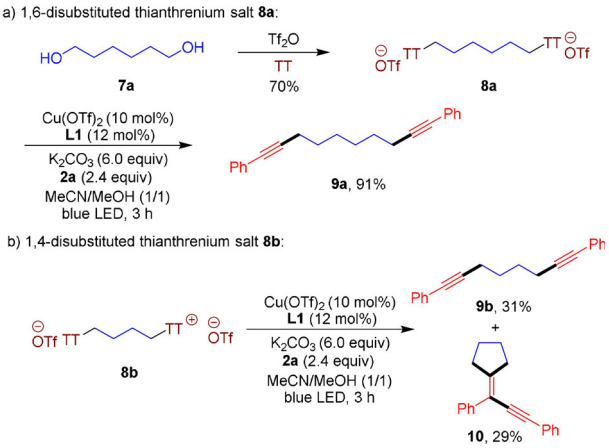
Table 3: Substrate scope of terminal alkynes.[a]



[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), **L1** (12 mol%), **1a** (0.20 mmol), **2** (0.24 mmol), K_2CO_3 (0.60 mmol), CH_3CN/MeOH (0.5 mL/0.5 mL), at room temperature, blue LED, under N_2, 3 h; yields are of isolated products. [b] DMF (1.0 mL), 12 h. [c] 12 h. [d] Using **1a** (3.6 equiv) in DMF.



Scheme 1. Methylation of alkynes with thianthrenium salt **4**.



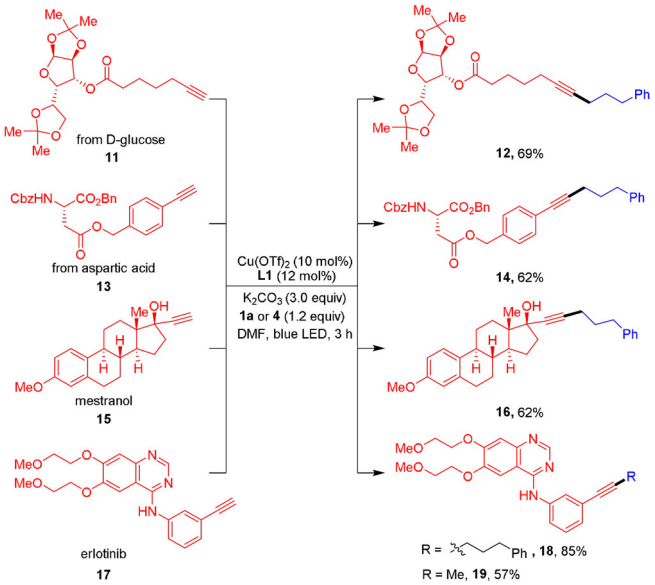
Scheme 2. Investigation of disubstituted thianthrenium salts.

(**2o**), pyridine (**2p**), and thiophene (**2q**), also exhibited high levels of reactivity. The reaction of silylacetylene **2r** with thianthrenium salt **1a** led to formation of product **3ar**, which can easily form a terminal alkyne after removal of the silyl protecting group. Moreover, alkyl-substituted alkynes **2s**–**2v** were also suitable substrates and produced unsymmetrical dialkyl alkynes in good yields. In particular, the reaction of **2v**, which contains a reactive hydroxy group for possible O-alkylation, showed extremely high selectivity for the formation of a C–C bond at the terminal alkyne position. In addition, the triple alkylation of substrate **1w** with three alkynyl groups produced product **3aw** in 42% yield.

The S-adenosylmethionine (SAM) superfamily is a family of sulfonium salts naturally found in the body, which can methylate complex molecules such as nucleic acids, proteins, and natural products in an S_N2 manner.[14] Inspired by this biosynthetic procedure, we used MeOTf and TT to prepare on a large scale thianthrenium salt **4** that bears a methyl group (Scheme 1).[15] Delightfully, the coupling of terminal alkynes **5a**–**5c** with reagent **4** afforded methylation products **6a**–**6c** in good to excellent yields.

Instead of using electroorganic synthesis to access 1,2-disubstituted thianthrenium salts from alkenes, [11] disubstituted thianthrenium salts can be produced from diols. For example, when diol **7a** was allowed to react with TT and Tf_2O, the desired 1,6-disubstituted thianthrenium salt **8a** was generated (Scheme 2). Disubstitution of this reagent with alkyne **2a** led to the corresponding diyne **9a** in 91% yield. Interestingly, the reaction of **2a** with a 1,4-disubstituted thianthrenium salt **8b** bearing a $(CH_2)_4$ linker generated diyne **9b**, with **10** as a by-product. The formation of **10** may proceed by a radical-mediated process through cyclization and trapping of the resulting vinyl radical.[16]

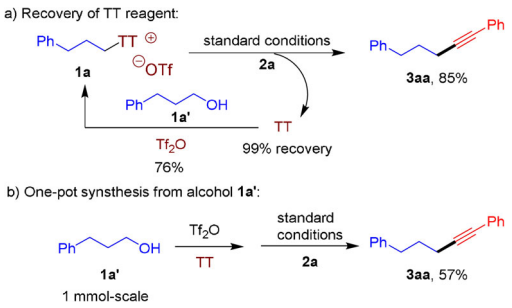
Alkyl thianthrenium salts can enable late-stage diversification of complex molecules as a range of functional units are tolerated (Scheme 3).[17] For example, the reaction of D-glucose derivative **11** with thianthrenium salt **1a** produced



Scheme 3. Late-stage modification of complex molecules.

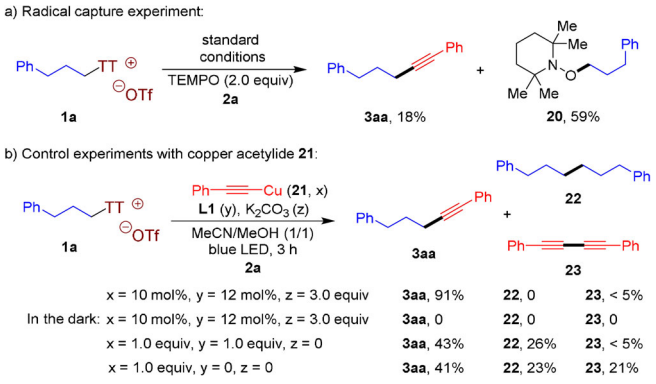
product **12** in 69% yield. Aspartic acid derivative **13** with a sensitive NH motif readily formed alkyne **14** without any racemization. The drug mestranol (**15**) bearing a terminal alkyne could be directly transformed with thianthrenium salt **1a** into internal alkyne **16** in 62% yield. Finally, the facile late-stage alkylation of erlotinib (**17**) by alkyl thianthrenium salts **1a** or **4** highlighted the robustness of the developed method.

We conducted additional experiments to improve the practicability and operability of this strategy (Scheme 4). The TT reagent can be efficiently recycled after the reaction (Scheme 4a). When alkyl thianthrenium salt **1a** is used in the cross-coupling reaction with alkyne **2a**, TT can be recovered in nearly quantitative yield. Furthermore, tandem reactions can start from alcohols to access alkynylation products (Scheme 4b). The reaction of alcohol **1a'** with TT and Tf_2O forms thianthrenium salt **1a**, which can further react with alkyne **2a** to afford **3aa** in 57% yield under the standard conditions.



Scheme 4. Further optimization of the operation procedures.

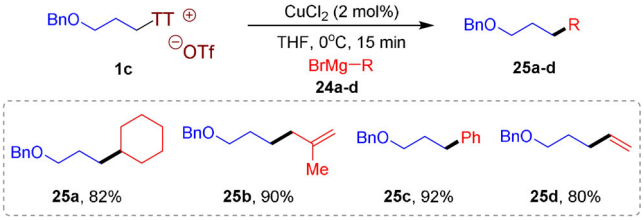
Further experiments were performed to gain insight into the reaction mechanism (Scheme 5). Adding TEMPO as a radical scavenger to a mixture of **1a** and **2a** led to the amount of product **1c** decreasing, with TEMPO-trapped adduct **20** isolated in 59% yield (Scheme 5a). The use of a presynthesized copper acetylide **21**[13f] as the catalyst for the reaction of substrates **1a** and **2a** led to product **3aa** being formed in excellent yield under irradiation with blue LEDs, thus indicating that it is a visible intermediate in the catalytic



Scheme 5. Mechanistic experiments.

cycle (Scheme 5b). Using a stoichiometric amount of complex **21** with the terpyridine ligand **L1** led to the formation of by-product **22** by dimerization of **2a**. Furthermore, the addition of the **L1** was found to be essential for inhibiting the formation of the alkyne homocoupling product **23**. In addition, a cyclic voltammetry study proved that the redox potential ($E_{1/2} = -1.20$ V vs. $Ag/AgNO_3$) of the excited complex formed between copper acetylide **21** and ligand **L1** is sufficiently strong to reduce thianthrenium salt **1a** ($E_{1/2} = -0.95$ V vs. $Ag/AgNO_3$; see the Supporting Information). Based on the above results and those of previous studies,[13,18] it is postulated that the excited copper acetylide species can reduce the thianthrenium salts to generate alkyl radicals, which is followed by formation of the $C(sp^3)$–$C(sp)$ bonds.

Alkyl thianthrenium salts can also be cross-coupled with Grignard reagents to build $C(sp^3)$–$C(sp^3)$ and $C(sp^3)$–$C(sp^2)$ bonds using a copper catalyst (Scheme 6). Different types of Grignard reagents, including alkyl (**24a**), allyl (**24b**), phenyl (**24c**), and vinyl reagents (**24d**), were coupled with thianthrenium salt **1c** and provided products **25a**–**25d** in excellent yields within 15 minutes. These examples demonstrate that alkyl thianthrenium salts can act as general alkyl sources in cross-coupling reactions.



Scheme 6. Further application of alkyl sulfonium salts in the Kumada reaction.

In summary, we identified that alkyl thianthrenium salts can undergo $C(sp^3)$–S bond cleavage and be used as alternative alkyl sources in cross-coupling reactions. The state-of-the-art application of alkyl thianthrenium salts in Sonogashira reactions is distinguished by its great functional breadth. We anticipate that alkyl thianthrenium salts will find immediate application in organic synthesis. The application of the above-mentioned alkyl reagents in other reactions is currently underway in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkynylation · copper · photoredox reactions · radical · sulfonium salts

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Communications

Coupling Reagents

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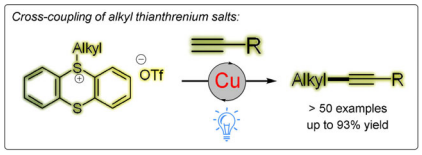
Enabling the Use of Alkyl Thianthrenium Salts in Cross-Coupling Reactions by Copper Catalysis



A series of thianthrenium salts have been developed that can undergo C(sp^3)–S bond cleavage and be used as reliable alkyl reagents. This ability has been demonstrated in copper-catalyzed Sonogashira and Kumada cross-coupling reactions under mild conditions.