Communication

Metal-free CH–CH-type cross coupling of arenes and alkynes di-rected by a multi-functional sulfoxide group

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Metal-free CH–CH-type cross coupling of arenes and alkynes directed by a multi-functional sulfoxide group

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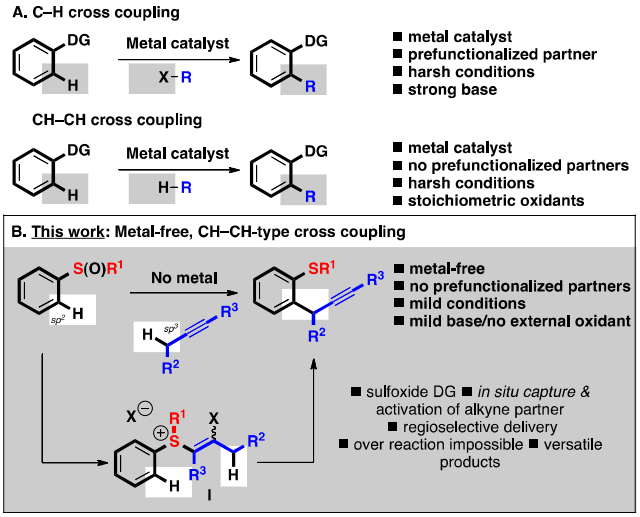
ABSTRACT: A metal-free CH–CH-type coupling of arenes and alkynes, mediated by a multi-functional sulfoxide directing group, exploits non-prefunctionalized coupling partners, proceeds under mild conditions, is operationally simple, and exhibits high functional group tolerance. The products of the CH–CH coupling are highly versatile and the metal-free process can be used for the construction and late-stage modification of important molecular scaffolds.

Carbon-carbon bond formation is a challenging objective that is essential in almost any synthetic endeavor that involves the construction or manipulation of molecular architecture.[1,2] In particular, metal-catalyzed C–H functionalization has become an established and more atom-economical way to construct C–C bonds with a wide selection of directing groups available to control processes involving C–H bonds on aromatic rings (Scheme 1A).[3] Furthermore, CH–CH-type cross coupling, so called cross-dehydrogenative coupling (CDC), has been developed that obviates the need for prefunctionalization of either coupling partner,[4] although issues of chemo- and regioselectivity, and a dependence on harsh conditions and stoichiometric oxidants remain issues that limit the broad take-up of such technology (Scheme 1B).[4] The majority of C–H cross coupling processes are mediated by platinum group metals and this leads to potential issues of supply risk[5] and metal contamination of products.[2a-c,6,7] Thus, despite remarkable recent advances in C–H cross coupling, the development of complementary, metal-free CH–CH-type cross coupling processes that use readily available non-prefunctionalized starting materials and that operate under mild conditions, is an outstanding challenge.

Here we report a metal-free CH–CH-type strategy that allows the selective coupling of aromatic centers to propargylic centers in alkynes at the expense of two C–H bonds – CAr(sp^2)–H and C(sp^3)–H bonds. A sulfoxide directing group in the arene plays a multi-functional role in the metal-free cross coupling, capturing, activating and delivering[8] the pronucleophilic alkyne partner, controlling the regiochemical outcome of the coupling, and ensuring that no over reaction takes place to give by-products (Scheme 1B).[9,10] Key to successful coupling is the proposed formation and rearrangement of alkenyl sulfonium salt intermediates **I**.[11] The products of cross coupling are challenging targets for current metal-mediated methods.

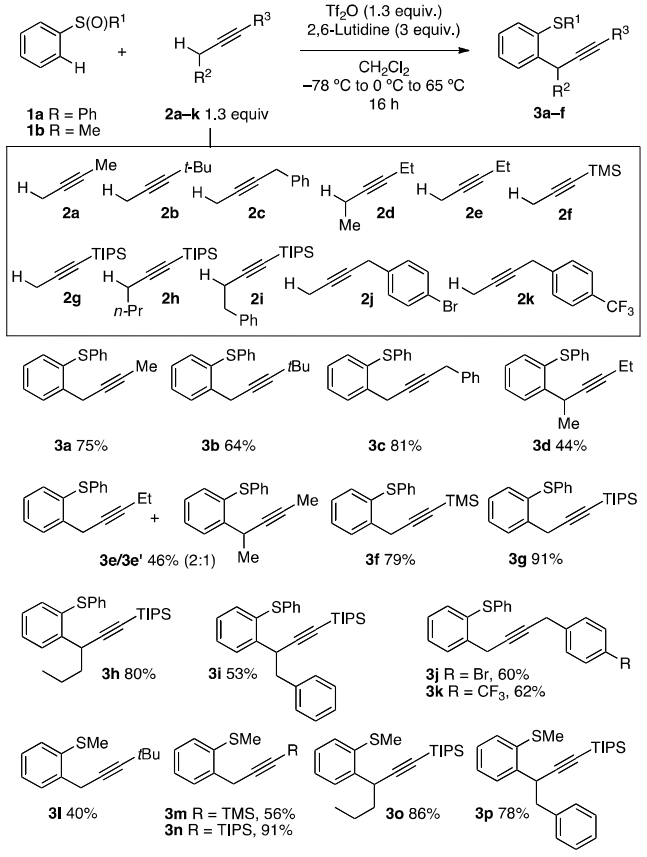


Scheme 1. A. Metal-catalyzed C–H and CH–CH cross coupling. B. Metal-free, CH–CH-type cross coupling of arenes and alkynes mediated by a sulfoxide directing group (DG). X–X = electrophilic activator of sulfoxide.

Our study began by investigating the cross coupling reaction between arene sulfoxide **1a** and butyne **2a** (See Supporting Information for optimization studies). Aiming to develop an operationally simple protocol, we explored the use of commercially available Tf_2O (1,1,1-trifluoromethanesulfonic anhydride) and 2,6-lutidine to mediate the proposed metal-free cross coupling.[8a] Unfortunately, in both MeCN and CH_2Cl_2, only traces of the desired product **3a** were observed. The role of the base and the temperature at which the activating agent was added were then investigated. Interestingly, if Tf_2O was added at –78 ºC in the presence of K_2CO_3, the desired

process was observed and a 65% isolated yield of the product of CH–CH-type coupling **3a** was obtained. When 2,6-lutidine was used as base and added at 0 ºC after 45 min, the cross coupling proceeded, delivering **3a** in good isolated yield (ca. 75%) after 16 h at 65 ºC (or 3 h with microwave heating).

Table 1. Alkyne substrate scope in the metal-free CH–CH-type cross coupling of alkynes with arenes bearing a sulfoxide directing group.[a]

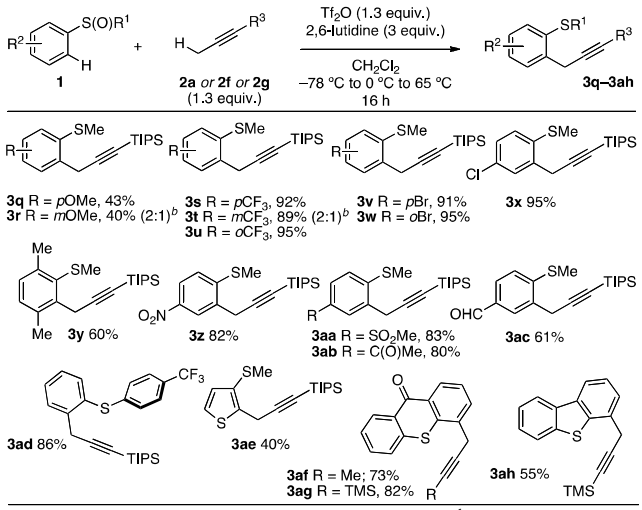


[a]Tf_2O (1.3 equiv.) was added to a mixture of **1** (0.15 mmol) and **2** (1.3 equiv.) in CH_2Cl_2 (0.2 M) at –78 °C. After 15 min at the same temperature, the mixture was stirred at 0 °C for 30 min. 2,6-Lutidine (3 equiv.) was then added. The reaction mixture was heated at 65 °C for 16 h.

Having optimized the reaction conditions, we next investigated the scope of the metal-free CH–CH-type cross coupling with regard to the alkyne partner. A range of readily available, simple and functionalized alkyne partners **2a**–**k** were employed in the study (Table 1). Arene sulfoxide **1a** underwent efficient coupling with sterically demanding 4,4-dimethylpent-2-yne **2b** and benzyl-substituted alkyne **2c** to give good isolated yields of the desired products **3b** and **3c**, respectively. Similarly, silyl-substituted alkynes **2f** and **2g** underwent efficient cross coupling to give versatile alkyne products **3f** and **3g**. Attractively, protected alkyne coupling products allow access to a range of products via deprotection and derivatization. Important bromide and CF_3 substituents in the alkyne were also compatible with the metal-free coupling (preparation of **3j** and **3k**). Pleasingly, challenging metal-free couplings involving secondary sp^3-propargylic C–H bonds were possible and resulted in new C–C bonds despite significant steric congestion: alkynes **2d**, **2e**, **2h** and **2i** underwent coupling to give branched coupling products **3d**, **3e'**, **3h**, **3i**, **3o** and **3p** in moderate to high yield. Finally, an arene bearing a methyl sulfinyl directing group could also be used in the cross coupling: treatment of **1b** with alkynes **2b**, **2f**, **2g**, **2h** and **2i** gave the desired coupling products **3l-p**, respectively (Table 1).

Cross coupling proceeded efficiently between a range of readily available starting arenes bearing a variety of substituents and alkynes **2a**, **2f** and **2g**. Arenes bearing electron-donating methoxy groups showed lower reactivity, leading to coupled products **3q** and **3r** in moderate yield. Less electron releasing methyl substituents on the arene were tolerated and **3y** was obtained in 60% yield. Electron-withdrawing groups on the arene partner were well tolerated in the metal-free CH–CH type cross coupling. For example, arene substrates bearing CF_3 groups in *ortho*, *meta* and *para* positions led to coupled products in excellent yield (**3s**–**3u**). Arenes containing bromide and chloride substituents also underwent coupling with high efficiency (**3v**, **3w** and **3x**). It is important to note that the presence of halides is often incompatible with metal-mediated cross coupling procedures.

Table 2. Study of arene substrate scope in the metal-free CH–CH-type cross coupling of arenes with alkynes.[a]



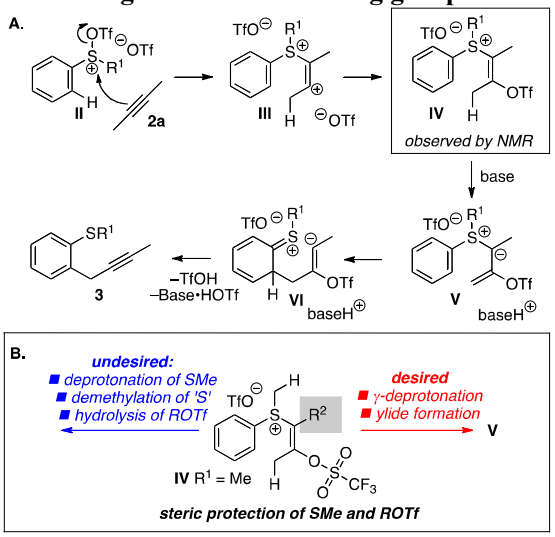
[a]See Table 1 for conditions. Isolated yields. [b]Ratio in brackets refers to regioselectivity. Alkylation away from the *meta* substituent gives the major product.

Nitro and sulfone substituents were also tolerated and arenes bearing these groups underwent successful coupling to give **3z** and **3aa**. The metal-free CH–CH-type cross coupling also proceeded in the presence of unprotected ketones and aldehydes: adducts **3ab**, **3ac**, **3af** and **3ag** were obtained in 61-82% yield. Substitution in the aryl unit of the sulfoxide-directing group was also toler-

ated with coupling taking place selectively on the more electron-rich ring (formation of **3ad**). Finally, heterocyclic coupling partners also underwent coupling with alkynes to give **3ae**, **3af**, **3ag** and **3ah** in moderate to good yield thus illustrating the potential of the process for the manipulation of heteroarene platforms (Table 2).

A possible mechanism for coupling with but-2-yne **2a** is shown in Scheme 2. The alkyne partner is captured and activated by the triflated sulfoxide **II** at low temperature[8-10] giving rise to vinyl triflate **IV** (*cf.* **I** in Scheme 1B). In the presence of base, **IV** may be deprotonated to give sulfonium ylide **V** and [3,3]-sigmatropic rearrangement of **V**[13] at elevated temperature followed by rearomatization delivers CH–CH-type cross coupling product **3**. In support of the above, quenching reactions between sulfoxide-bearing arenes **1a** and **1b** and alkyne **2a** at 0 °C prior to the addition of base, resulted in complete conversion to alkenylsulfonium salts (see Supporting Information).[11,12]

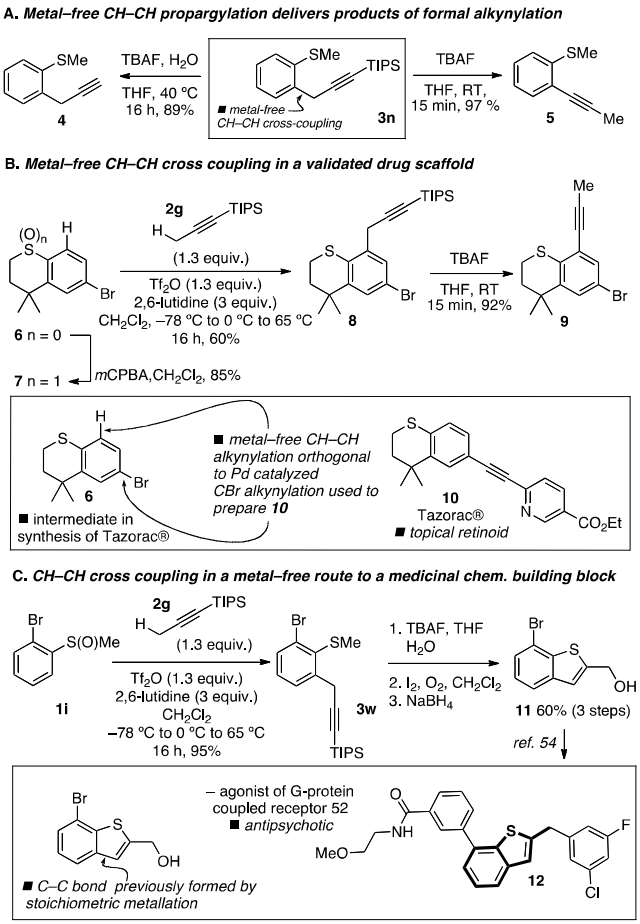
Scheme 2. Proposed mechanism for the metal-free CH–CH-type cross coupling of but-2-yne 2a with arenes bearing a sulfoxide directing group.



The selective onwards reaction of alkenylsulfonium intermediate **IV** (R^1 = Me) is key to the success of the cross coupling. Alkynes bearing large substituents are particularly effective as they control the regiochemistry of the addition to the activated sulfoxide **II** and give rise to alkenylsulfonium intermediates **IV** bearing large R^2 groups.[14] These large R^2 groups block undesired deprotonation and nucleophilic demethylation of the SMe group, and hydrolysis of the triflate in **IV**.[11]

The products of cross coupling are versatile building blocks for organic synthesis and are difficult to access selectively using current methods. Focusing on metal-free transformations,[15] deprotection of adduct **3n** delivered **4** or isomerization product **5**, depending on the conditions employed. Notably, arylalkyne **5** is the product of a formal metal-free, C–H Sonogashira-type reaction (Scheme 3A).[16]

Scheme 3. Sulfoxide-directed metal-free CH–CH-type cross coupling for scaffold construction and late-stage modification.



Pleasingly, a sulfur atom in a validated drug scaffold can be used to direct the metal-free CH–CH cross coupling. Sulfide scaffold **6** is an intermediate in the synthesis of the topical retinoid Tazarotene (Tazorac®) **10**.[17] Activation of **6** by sulfur oxidation and CH–CH cross coupling with alkyne partner **2g** gave **8** in good yield. High yielding deprotection/isomerization then gave alkynylation product **9**. Attractively, the metal-free sulfoxide directed CH–CH coupling is orthogonal to the Pd-catalyzed alkynylation of the C–Br bond used in the preparation of the drug (Scheme 3B).[17,18] Functionalized benzothiophene **11** is a key intermediate in the synthesis of the antipsychotic drug **12**: an agonist of the G-protein coupled receptor 52.[19] The crucial C–C bond in **11** is typically prepared by stoichiometric metallation of the arene.[20] The sulfoxide-directed CH–CH process allows medicinally-relevant benzothiophene **11** to be prepared from **1i** in 4 metal-free steps: CH–CH cross coupling, TBAF deprotection, I_2-mediated heterocyclization,[21] and $NaBH_4$ reduction of the intermediate benzothiophene aldehyde delivers **11** in 57% overall yield (Scheme 3C).

In summary, we have developed an operationally simple, metal-free CH–CH-type cross coupling of arenes and alkynes that proceeds under mild conditions. The process is mediated by a sulfoxide-directing group that captures and activates the alkyne coupling partner before delivery to the arene and C–C bond formation. The products of cross coupling are difficult to access using current metal-mediated procedures and are rich in synthetic potential. For example, they are readily converted to products of formal metal-free arene C–H alkynylation and to important benzothiophene motifs, as exemplified by the metal-free synthesis of a precursor to an antipsychotic drug. Furthermore, sulfur in a validated heterocyclic drug scaffold can be used to direct metal-free CH–CH cross coupling thus facilitating late-stage scaffold elaboration.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Optimization table, mechanistic studies, experimental details, characterization data and spectra are in the Supplementary Information (PDF).

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TOC graphic


S(O)R1
H
R3
H
R2
Tf2O
base
SR1
R3
R2
35 examples
up to 95% yield
sulfoxide-directed metal-free CH–CH-type cross coupling
no metals ■ no prefunctionalized partners ■ mild conditions ■ versatile products