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Cobalt-Catalyzed Reductive Cross-Coupling to Construct Csp³-Csp³ Bonds via Csp³-S and Csp³-X Bonds Activation

Meng-Yu Gao,^a Corinne Gosmini^{a*}

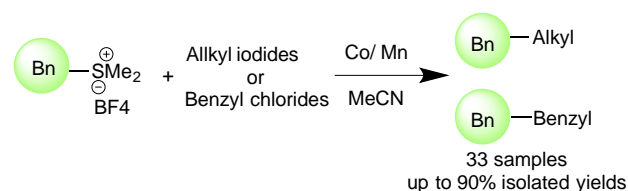
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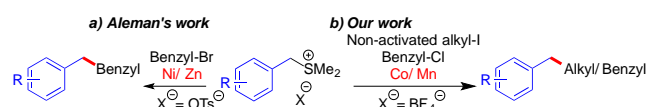
ABSTRACT: A cross-electrophilic coupling of benzyl sulfonium salts with alkyl halides forming Csp³-Csp³ bonds is described using a Co-based catalytic system. The activation of the stable Csp³-S bond of benzyl sulfonium salts under mild reaction conditions leads to various functionalized alkyl derivatives. Preliminary mechanistic studies suggest the involvement of alkyl radicals both formed from alkyl halides and benzyl sulfoniums through a single electron transfer.

The construction of carbon-carbon bonds is important in synthetic organic chemistry but also in materials and biology. Thus, transition metal-catalyzed cross-coupling reactions have been extensively studied over the past decades and recognized with the Nobel Prize in Chemistry in 2010 for the development of palladium-catalyzed cross-coupling reactions.¹ Most of the cross-coupling reactions imply a nucleophilic organometallic reagent, such as for example Grignard reagents, organozinc, or organoboron derivatives, and an electrophile in the presence of a transition metal.^{1a,2} However, to avoid the need or preformation of stoichiometric, reactive, and often sensitive organometallic species, especially when a reactive functional group is present, electrophilic reductive cross-coupling reactions have been developed since the beginning of this century to form a C-C bond in only one step. This interesting procedure exhibits high functional group compatibility, regioselectivity, and chemoselectivity. In most cases, these cross-coupling reactions involve organohalides as electrophiles.³ However, in order to reduce halogen wastes, other electrophiles such as C-O (alcohol derivatives: sulfonates,⁴ esters,⁵ carbonates,^{5d,6} oxalates⁷, *etc.*), C-N (amine derivatives, such as pyridinium salts,⁸ ammonium salts,⁹ *etc.*), C-S (sulfonium salts¹⁰), as well as carboxylic acid derivatives (N-hydroxy phthalimide esters¹¹) have been more recently involved in Ni, Cu or Co catalyzed cross-couplings. Moreover, although the formation of Csp²-Csp² bonds between two Csp² electrophiles is well established,^{3g,12} the Csp³-Csp³ bond formation from two Csp³ electrophiles remains much more challenging while these bonds are ubiquitous in molecules. Indeed, the unwanted facile β -hydride elimination from alkyl metal complexes is a key impediment to efficient cross-coupling of alkyl electrophiles. In the case of Co-catalyzed cross-couplings involving benzylic substrates such as benzyl chloride^{3d}, benzyl zinc¹³, and benzyl mesylates^{4b}, Csp² partners were always employed. Howev-



er, some electrophilic cross-couplings have been already developed between two different alkyl compounds using Ni or Co as catalysts^{3b, c, 14} and notably benzyl sulfonium salts.¹⁵ In particular, Aleman and our group showed recently that these compounds could react by reductive cross-coupling with activated alkyl halides.¹⁶ Aleman reported the cross-coupling with benzyl bromides using a nickel catalyst^{16a} (**Scheme 1a**) while allylic acetates or ethers were used by our group under cobalt catalysis^{16b}. Nevertheless, compared to the widely used C-O or C-N electrophiles, sulfonium salts still did not receive much attention in cross-coupling reactions since Liebeskind's reports^{10a, b}, although S-containing motifs are very present in drugs and materials.¹⁷ These salts are bench-stable and can be synthesized easily and economically from alcohols, organohalides, thiols, or thioethers.^{15a, b} They can smoothly undergo oxidative addition with transition metal catalysts and release a neutral sulfide instead of anionic sulfur fragments limiting the risk of catalyst poisoning. In the development and application of sulfonium salts in cross-coupling, different elegant reactions were reported such as C-H arylation¹⁸, alkylation/ alkenylation¹⁹, and carbonylation²⁰. Hence, considering that no cross-electrophilic coupling was reported between non-activated alkyl halides and benzyl sulfonium salts, regardless of the catalyst, we envisioned the Co-catalyzed reductive cross-coupling of benzyl sulfonium salts with non-activated alkyl iodides and the extension to activated benzyl chlorides (**Scheme 1b**).

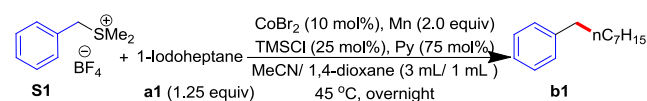
Scheme 1. Reductive cross-couplings of benzyl sulfonium salts with alkyl halides.



The Co-catalyzed cross electrophilic-coupling of benzyl sulfonium salts (**S1**) with an alkyl iodide such as 1-iodoheptane (**a1**) led to a 41% GC yield of the desired product (1-phenyloctane) **b1** in allylation conditions we previously reported. (see SI for more details).

Then, numerous experiments were conducted to improve this cross-electrophilic coupling (see SI for more details). As shown in **Table 1**, the combination of 10 mol% of CoBr₂, 2.0 equivalents of Mn activated by 25 mol% of TMSCl, with addition of 75 mol% of pyridine in a mixture of MeCN/ 1,4-dioxane led to a 60% GC yield of the desired product **b1** at 45 °C overnight. With MeCN or 1,4-dioxane as the sole solvent, yields of 1-phenyloctane **b1** decreased to 48% or 11% respectively, but the formation of the homo-coupling from **a1** was significantly inhibited in sole 1,4-dioxane (**Table 1, entries 2, 3**). In the mixture of MeCN and 1,4-dioxane, the quantity of 1,4-dioxane, is importante (**Table 1, entries 4, 5**). With other solvents in place of MeCN, like THF, DMA, and MeOH, the yield of **b1** was lower. (**Table 1, entries 6-8**). Decreasing the amount of CoBr₂ to 5% gave a similar yield of **b1** (62% GC yield, **Table 1, entry 9**). In this condition, decreasing the amount of Mn or using Zn instead of Mn affected the efficiency of the cross-coupling significantly (**Table 1, entries 10, 11**). Moreover, at a higher or lower temperature (60 °C or rt), a low yield of **b1** was obtained together with more dibenzyl or remaining **a1** (**Table 1, entry 12, 13**). However, extending the reaction time to 24 h at rt, the yield of **b1** increased to 73% (**Table 1, entry 14**). Cobalt salt and Mn were necessary for this alkylation reaction but a of **b1** was formed (33% GC yield) even in the absence of pyridine. Scaling up the reaction to 10 mmol led to 78 % GC yield (65% isolated yield). Finally, no reaction occurred upon replacing CoBr₂ by NiBr₂ under the condition (see SI- **Table 3.5**).

Table 1. Optimization of Reaction Conditions of benzyl dimethyl sulfonium salt (**S1**) with 1-iodoheptane (**a1**).^a



Entry	Variation	b1 yield/%
1	None	60
2	MeCN (0.5 M)	48
3	1,4-dioxane (0.5 M)	11
4	MeCN/ 1,4-dioxane (3.5 mL: 0.5 mL)	56
5	MeCN/ 1,4-dioxane (2.0 mL: 2.0 mL)	30
6	THF (0.5 M)	36
7	DMA (0.5 M)	Trace
8	MeOH (0.5 M)	25
9	CoBr ₂ (5 mol%)	63
11	Mn (1.5 equiv)	11 ^b
11	Zn (2.0 equiv)	20 ^b
12	60 °C	43 ^b
13	rt	40 ^b
14	CoBr ₂ (5 mol%), rt, 24 h	73/66 (57 ^c)

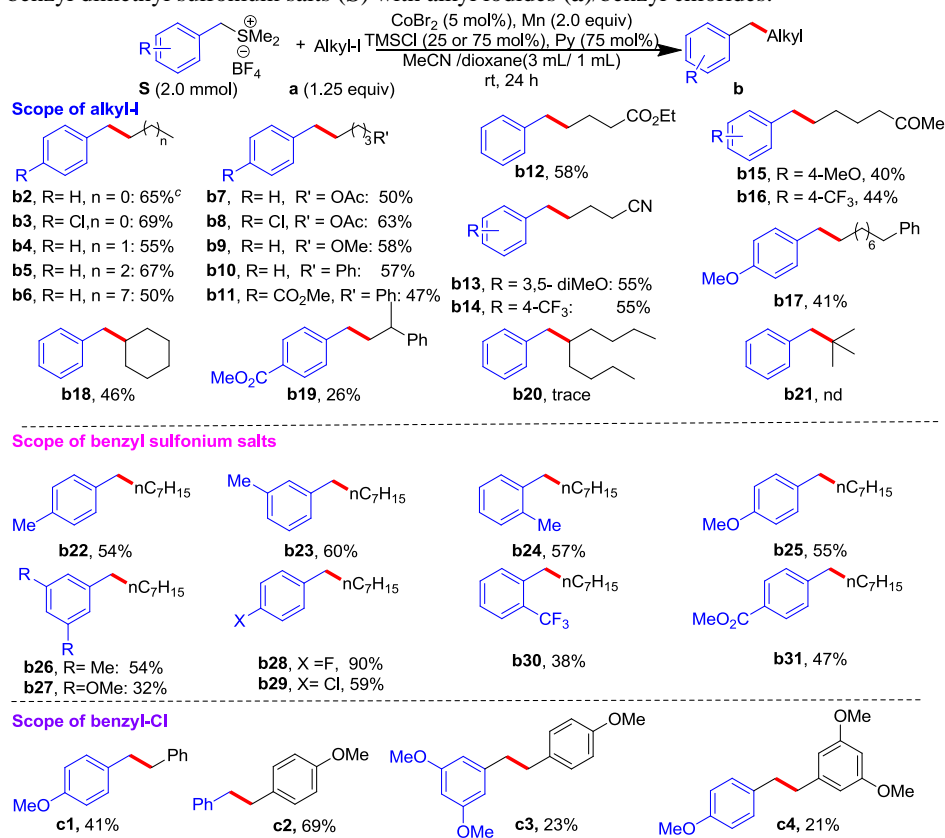
^a Reactions were performed with **S1** (2.0 mmol), **a1** (2.5 mmol), Mn (2.0 equiv), pyridine (75 mol%), TMSCl (25 mol%) in MeCN/1,4-dioxane under N₂, GC yields using decane as an internal standard. ^b CoBr₂ (5 mol%). ^c Isolated yield.

The nature of the sulfonium partner was modified: benzyl dimethyl sulfonium bromide and 1-benzyl tetrahydro-1H-thiophen-1-ium hexafluorophosphate formed **b1** in respectively 10% and 56% yield under the optimized condition defined in **Table 1**. To compare with other benzylic electrophiles, benzyl chloride gave a similar yield as the benzyl sulfonium salt **S1**, while only a trace amount of **b1** was detected with the more reactive benzyl bromide. Among C-O electrophiles, benzyl carbonate was unreactive, and benzyl sulfonates (mesylate or tosylate) only gave trace or a low yield of the desired coupling product.

With the optimized conditions described in **Table 1** in hand, the scope of benzyl sulfonium tetrafluoroborate salts with various alkyl iodides was studied (**Table 2**). As shown, a large number of substituted non-activated alkyl iodides and functionalized benzyl sulfonium salts reacted under the established conditions with either 25 or 75 mol% of TMSCl. It is obvious that this method is general for primary alkyl iodides, providing a wide range of cross-coupling products in moderate to good isolated yields. For unsubstituted primary linear alkyl iodides, 50% to 69% yields of the cross-coupling products were obtained (**b2-b17**). Alkyl iodides with various functionalities, such as acetate (**b7, b8**), ether (**b9**), phenyl (**b10, b11, b17**), and ester (**b12**), were well tolerated. A functional group could be tolerated both on the benzyl sulfonium salt and the primary alkyl iodide (**b13- b16**). In contrast, cross-couplings of secondary or tertiary alkyl iodides with benzyl sulfonium salt led to only traces or few of products. (**b19-b21**) due to their higher reactivity except for the coupling with cycloalkane such as iodocyclohexane delivering the desired product **b18** in 46% isolated yield.

Although different functionalized groups on the benzyl moiety of sulfonium salts were well tolerated, the coupling of 1-iodoheptane (**a1**) with electron-donating groups substituted benzyl sulfonium salts leading to **b22-b25** was more efficient than with electron-withdrawing groups substituted benzyl sulfonium salts (**b30, b31**) because of the competitive homocoupling of the benzyl sulfonium salt. Halides (F or Cl) also led to cross-coupling products in good yields (**b28, b29**). The steric hindrance on the benzyl sulfonium salt did not affect the cross-coupling (**b22-b24**). Several electron-donating groups on the aromatic ring were also allowed (**b26, b27**).

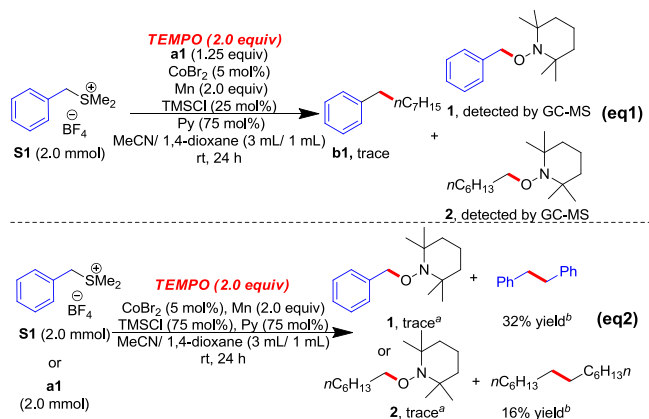
Finally, we extended the cross-coupling of benzyl sulfonium tetrafluoroborate salts with benzyl chlorides (**Table 2**). In contrast to the work carried out by Aleman^{16a}, benzyl chloride showed good and even better efficiency than benzyl bromide in this Co-catalyzed Csp³-Csp³ bond-forming reaction. With a methoxy substituted benzyl chloride, the yield increased significantly compared to the same substituent on the benzyl sulfonium salt (**c1, c2**). These results prompted us to attempt the synthesis of a dihydro resveratrol precursor - a key intermediate in the inhibition of pancreatic oxidative damage²¹. However, the cross-coupling product yields (**c3, c4**) were moderate and similar, regardless of the entity bearing the two methoxy groups.

Table 2. Scopes of benzyl dimethyl sulfonium salts (**S**) with alkyl iodides (**a**)/benzyl chlorides. ^{a b}

^a Standard condition: **S** (2.0 mmol), **a** (2.5 mmol), CoBr₂ (5 mol%), Mn (2.0 equiv), pyridine (75 mol%), TMSCl (25 or 75 mol%) in MeCN (3.0 mL) and 1,4-dioxane (1.0 mL) at rt, 24 h, N₂. ^b Isolated yield. ^c GC yield.

To investigate the mechanism of this Co-catalyzed reductive Csp³-Csp³ bond-forming process, a few experiments were conducted. At the outset, the addition of 2 equivalents of 2,2,6,6-tetramethylpiperine-1-oxyl (TEMPO) in the alkylation reaction between **S1** and **a1** inhibited significantly the coupling (**Scheme 2**). Only a trace amount of **b1** was detected by GC-MS, along with trace amounts of the TEMPO-trapped products **1** and **2** (**eq 1**). Moreover, the reaction of either **S1** or **a1** in the presence of TEMPO (**eq 2**), led to traces of 1-(benzyloxy)-2,2,6,6-tetramethyl-piperidin (**1**) or 1-(heptyloxy)-2,2,6,6-tetramethyl-piperidine (**2**) detected by GC-MS as well as either the dimerization product of **S1** (32% GC yield of dibenzyl) or **a1** (16% GC yield of tetradecane) respectively. Likewise, adding glavinoxyl free radical in the reaction between **S1** and **a1** led to a significantly decreased cross-coupling product yield when increasing the amount of free radical reagent (see SI). These results suggested that both benzyl and alkyl radicals were involved in this Co-catalyzed alkylation reaction.

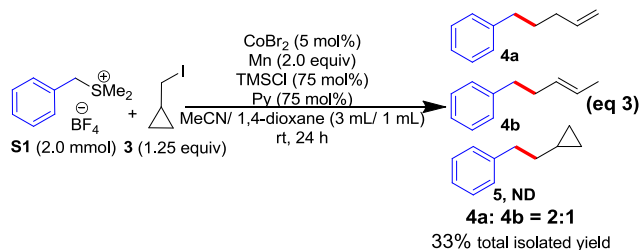
Scheme 2. TEMPO trapping experiments with alkyl iodide.



^a detected by GC-MS. ^b GC yields using decane as an internal standard.

To confirm this hypothesis, iodomethylcyclopropane (**3**) was coupled with **S1** under the optimized alkylation condition (**Scheme 3**, **eq 3**). A mixture of ring-opened products **4** [5-phenylpent-1-ene **4a** and (*E*)-3-pentenyl benzene (**4b**)] was obtained in 33% isolated yield, without unrearranged cross-coupling product (**5**).

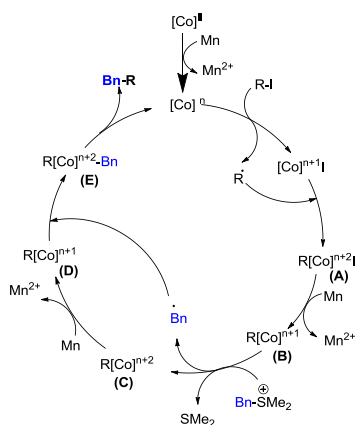
Scheme 3. Radical clock trapping experiments.



These results prompted us to propose a mechanism (**Scheme 4**) based on our previous reports related to the $\text{Csp}^3\text{-Csp}^3$ homocoupling.²² The cross-coupling of benzyl sulfonium salts and benzyl chlorides suggested a lower reactivity of benzyl sulfonium salts compared to benzyl chlorides. Thus, we proposed that the alkyl radical from the alkyl iodide formed prior to the benzyl radical from sulfonium salt.

First, the catalytic cycle starts with the reduction of the Co(II) pre-catalyst by the manganese into an active low-valent Co species. Then, the oxidative addition of the low-valent Co species with an alkyl radical generated from the alkyl iodide leads to a cobalt complex **A**. After subsequent reduction by Mn , the formed alkyl complex **B** undergoes one electron transfer to benzyl sulfonium salt, delivering Co complex **C**, a benzyl radical and a thioether. Co complex **C** reduced another time by manganese, lead to Co complex **D**. Finally, the benzyl alkyl Co complex **E**, generated by the combination of the benzyl radical and the low-valent Co complex **D**, provides the cross-coupling product by reductive elimination along with the regeneration of the active Co species.

Scheme 4. Proposal mechanism



In conclusion, we have demonstrated that benzyl sulfonium salts are suited for the construction of $\text{Csp}^3\text{-Csp}^3$ bonds with non-activated alkyl iodides or benzyl chlorides via a Co -catalyzed reductive cross-coupling. Compared to other Co -catalyzed reductive cross-coupling, a mixture of acetonitrile and dioxane as solvent was necessary to obtain best yields. A large variety of functionalized benzyl sulfonium salts reacted with a broad range and small excess of primary or cyclic secondary alkyl iodides in moderate to good yields. To the best of our knowledge, it is the first report using sulfonium salts as electrophiles in metal-catalyzed reductive cross-coupling with non-activated alkyl halides to build $\text{Csp}^3\text{-Csp}^3$ bonds. Mechanistic studies suggested both the generations of benzyl and alkyl radicals

from benzyl sulfonium salts and alkyl iodides respectively. Further studies aiming at using other sulfonium salts in cobalt-catalyzed C-C bond formation and gaining detailed mechanistic insights are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

brief description (file type, i.e., PDF)

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