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Copper-Catalyzed Cross-Coupling of Alkylsamarium Reagents with Alkyl Halides

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Abstract: SmI_2/HMPA converts alkyl iodides and bromides to alkyl samarium reagents which can be cross-coupled with primary alkyl iodides and bromides and secondary iodides in the presence of Cu(I) halides or Li_2CuCl_4 at room temperature. The alkylation of primary iodides gives good yields of cross-coupling products with negligible homo-coupling products. The method is especially useful for the small scale cross-coupling reactions. © 1997 Elsevier Science Ltd.

The development of samarium (II) reagents for the reduction of organic functional groups and for carbon-carbon bond formation has received a great deal of attention[1] since Kagan and coworkers developed a convenient synthesis of SmI_2 and provided an outline of its reactivity with organic functional groups.[2] It is believed that the reduction of alkyl halides by SmI_2/HMPA[1c, 3] or $Sm(OTf)_2$[4] under "Grignard" conditions forms organosamarium (III) intermediates. The development of copper catalyzed conjugate additions of such reagents by Curran and Wipf[5] led us to wonder if they might also be used for copper catalyzed cross coupling of alkyl halides. This is indeed the case, as summarized in Tables 1 and 2.

Table 1. Cross-coupling of alkyl halides catalyzed by different copper salts[a]

Entry	RX	R'X	catalyst	RR'[c]	RR[b]	R'R'[c]
1	n-$C_7H_{15}Br$	n-$C_6H_{13}I$	CuBr	90	0	3
2	n-$C_7H_{15}Br$	n-$C_6H_{13}I$	CuCl	77	3	8
3	n-$C_7H_{15}Br$	n-$C_6H_{13}I$	CuI	68	8	3
4	n-$C_7H_{15}Br$	n-$C_6H_{13}I$	Li_2CuCl_4	75(85[d])	5	2

2.5 eq SmI_2, 8.3 eq of HMPA, 1.0 eq of RX, 0.17 eq of catalyst, and 0.83 eq of R'X, 15 min., room temperature. [a] Yields were determined by GC. Structures and yields were identified by GC/MS comparison with known materials [b] Yield based on RX. [c] Yield based on R'X
[d] 1.0 eq of RX and 0.5 eq of R'X were used. na: volatile or non-volatile material.

From Table 1, it can be seen that CuBr is the most effective catalyst for cross-coupling (90%). CuCl and CuI gave moderate yields of cross-coupling product (Entries 2,3). Li_2CuCl_4 (0.1 M in THF) also gave good results, and was easier to handle. Replacement of CuBr with $FeCl_3$ or $ZnCl_2$ in the above experiments failed to give any homo or cross-coupling product. In the absence of Cu catalyst, no coupling was observed.

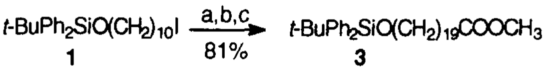
Table 2. Cross-coupling of several alkyl halides, catalyzed by CuBr [a]

Entry	RX	R'X	RR' [c]	RR [b]	R'R' [c]
1	n-$C_7H_{15}I$	n-$C_6H_{13}I$	87(92[d])	5	1
2	2-bromoheptane	n-$C_6H_{13}I$	48(60[e])	0	2
3	n-$C_6H_{13}I$	n-$C_7H_{15}Br$	9	3	0
4	n-$C_{10}H_{21}Br$	n-C_3H_7Br	63[f]	0	na
5	n-$C_6H_{13}I$	$C_6H_5CH_2Br$	32	9	na
6	$C_6H_5CH_2Br$	n-$C_6H_{13}I$	53	na	8
7	n-$C_{10}H_{21}Br$	2-iodopropane	51[e]	na	na

Reaction conditions as in Table 1. [a,b,c,d] as in Table 1. [e] 6 h. [f] 20 h.

From Table 2, it can be seen that coupling of primary or secondary alkyl samaium reagents, from bromides or iodides, with primary iodides affords useable yields of cross coupling products with little or no homocoupling by-product. On the other hand, coupling of a primary alkyl samarium with benzyl bromide or isopropyl iodide is less efficient, and is useless with an alkyl bromide. We also tried to make organosamarium reagents from iodobenzene, bromobenzene, methyl 2-bromoacetate, methyl 3-bromopropanoate, the tosylate of hexan-1-ol, and 1,6-dibromohexane, and then couple them with 1-iodohexane, but in no case was a cross coupling product observed. Although alkyl samarium "Grignard" reagents appear to react with ester groups,[3c,6] here, coupling via the copper derivative with an ω-iodoester was quite efficient, as shown in Scheme 1.

Scheme 1[7]



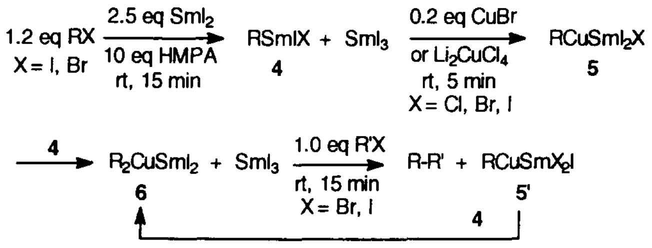
a) **1**: 1.0 eq; SmI_2: 2.5 eq; HMPA: 10 eq, rt, 15 min

b) CuBr: 0.2 eq, rt, 5 min

c) $I(CH_2)_9COOCH_3$ (**2**: 0.84 eq), rt, 30 min

The mechanism proposed by Totleben, Curran and Wipf[5a] for the copper catalyzed conjugate addition of alkyl samarium reagents may be adapted to the cross-coupling reaction, as shown in Scheme 2.

Scheme 2



Alkylsamarium **4** is the presumed product of the reduction of alkyl iodides or bromides in THF/HMPA at room temperature.[1c] Alkylsamarium **4** is transmetalated smoothly *in situ* to monoalkyl copper samarium species **5**. The nucleophilic ability of this species is apparently only marginal.[5a] It then reacts with a second equivalent of organosamarium reagent **4** to form a dialkylsamarium copper complex **6**. It is this complex **6** which reacts with another alkyl halide to give the cross-coupling product. Because the by-product of the coupling reaction, **5'**, can combine with another equivalent organosamarium reagent **4** to regenerate dialkylsamarium copper complex **6**, only a catalytic amount of the catalyst is needed. In fact, when 1 full equivalent of copper salt was used, no cross coupling product was observed, presumably because there was not sufficient RSmIX **4** to form the active dialkylsamarium copper complex **6**.

In a typical experiment, 0.1 M SmI_2 in THF was made from Samarium and iodine.[6b] To a solution of 15 mL (1.5mmol) of 0.1 M SmI_2 in THF under argon was added 0.87 mL (5 mmol) of HMPA. The deep purple solution was stirred at rt for 5 min and 1-bromoheptane (94 μL, 0.60 mmol) was added. The resulting light purple solution was stirred for 15 min and 14 mg (0.1 mmol) of CuBr was added, followed, after 5 min, by 74 μL (0.50 mmol) of 1-iodohexane. The resulting mixture was stirred for 15 min. The reaction mixture was poured into a mixture of 20 mL of brine and 5 mL of 10% HCl. The organic phase was separated and the aqueous phase was extracted with ether (3x30 mL). The combined organic layers were washed with saturated sodium thiosulfate, brine, dried, and concentrated. The organic layer was analyzed by GC.

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7. Both **1** and **2** were made from commercially available methyl 10-hydroxydecanoate.
1: ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.05 (s, 9H), 1.20-1.40 (m, 12H), 1.50-1.60 (m, 2H), 1.75-1.85 (m, 2H), 3.18 (t, J=6.5Hz, 2H), 3.65 (t, J=7.0Hz, 2H), 7.30-7.40 (m, 6H), 7.60-7.65 (m, 4H). Anal. Calcd. for $C_{26}H_{39}IOSi$: C, 59.76; H, 7.52; I, 24.28. Found: C,60.08; H, 7.55; I, 24.48.

   2: IR ($CDCl_3$) 1731.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz) δ 1.25-1.40 (m, 10H), 1.56-1.66 (m, 2H), 1.78-1.85 (m, 2H), 2.30 (t, J=7.5Hz, 2H), 3.19 (t, J=8.1Hz, 2H), 3.67 (s, 3H). Anal. Calcd. for $C_{11}H_{21}O_2I$: C, 42.32; H, 6.78; I, 40.46. Found: C, 42.47; H, 7.02; I, 40.45.

   3: IR ($CDCl_3$) 1731.6 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400MHz) δ 1.05 (s, 9H), 1.15-1.35 (m, 30H), 1.50-1.65 (m, 4H), 2.30 (t, J=7.5Hz, 2H), 3.65 (t, J=6.6Hz, 2H), 3.66 (s, 3H), 7.35-7.42 (m, 6H), 7.62-7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 19.22, 23.85, 23.90, 24.97, 25.78, 26.87, 28.85, 28.94, 29.17, 29.27, 29.40, 29.47, 29.62, 29.64, 29.66, 29.69, 29.71, 32.59, 34.12, 51.43, 64.02, 127.55, 129.46, 134.19, 135.57, 174.33; ESI-MS 581.3 $(M+H)^+$. Anal. Calcd. for $C_{37}H_{60}O_3Si$: C, 76.49; H, 10.41. Found: C, 76.78; H, 10.29.

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