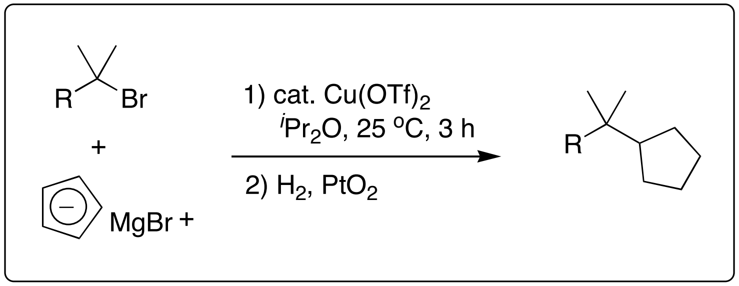
Copper-Catalyzed Reaction of Alkyl Halides with Cyclopentadienylmagnesium Reagent



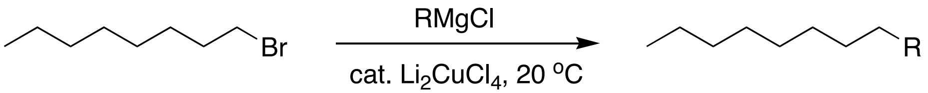
Masahiro Sai, Hidenori Someya, Hideki Yorimitsu, and
Koichiro Oshima
Organic Letters ASAP (4/11/2008)

Wipf Group Current Literature
Jennie Kravchenko - 05/31/08

Copper-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Primary Alkyl Halides

Alkyl Bromides:

Tetrahedron **2000**, 56, 2737



Alkyl Fluorides:

J. Am. Chem. Soc. **2003**, 125, 5646

$$\underset{\text{R = alkyl}}{\text{R}-\text{F}} \quad + \quad \underset{\text{R' = alkyl, aryl}}{\text{R'}-\text{MgX}} \xrightarrow[\text{1,3-butadiene}]{\text{cat. CuCl}_2} \text{R}-\text{R'}$$

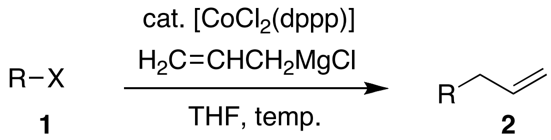
Alkyl Chlorides:

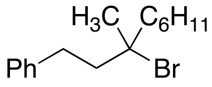
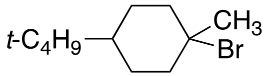
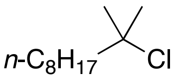
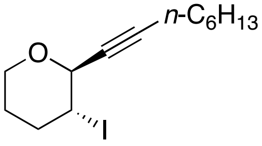
Angew. Chem. Int. Ed. **2007**, 46, 2086

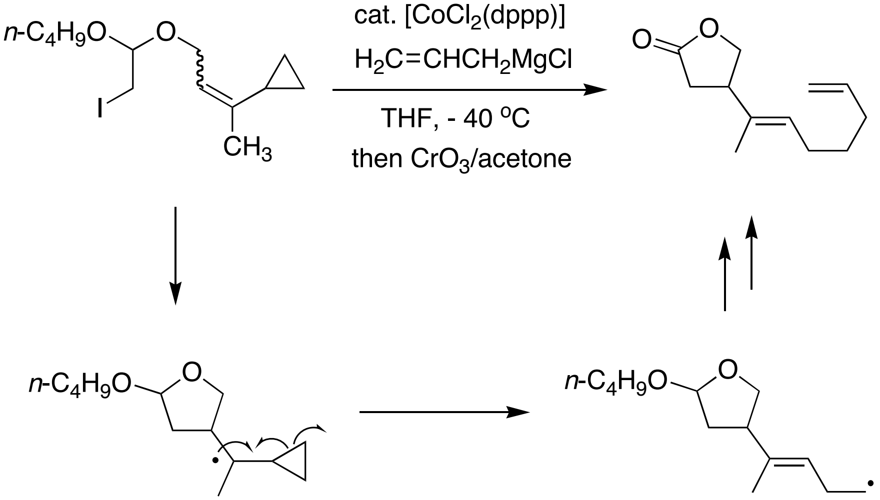
$$\text{Alkyl}-\text{Cl} \quad + \quad \text{R}-\text{MgX} \xrightarrow[\text{THF}]{\substack{\text{cat. CuCl}_2 \\ \text{cat. Ph}-\!\equiv\!-\text{Me}}} \text{Alkyl}-\text{R}$$

Cobalt-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Secondary and Tertiary Alkyl Halides

Substrate Scope:



1	Temperature (°C)	Yield of **2** (%)
	- 20	83
	0	76
	20	31
	- 40	76



- $[CoCl_2(dppp)]$ effectively catalyzes such reactions of secondary and tertiary alkyl halides with allylic Grignard reagents

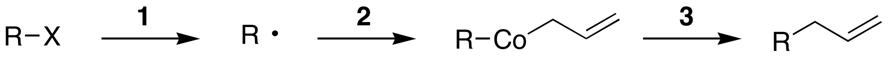
- Treatment of substrate with allyl Grignard reagent in the presence of $[CoCl_2(dppp)]$ furnished the ring-opening product

- Existence of radical intermediates account for such ring opening

Angew. Chem. Int. Ed. **2002**, 41, 4137

Cobalt-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Secondary and Tertiary Alkyl Halides

Proposed Mechanism:



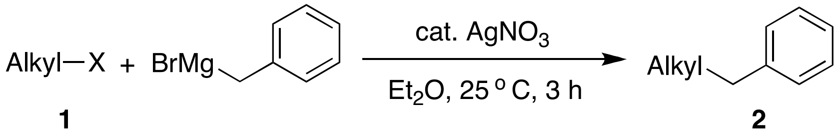
1) Single-electron transfer from cobalt complex
2) Recombination of alkyl radical and cobalt complex
3) Reductive elimination

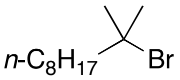
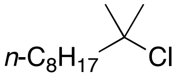
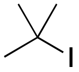
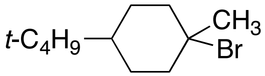
- π-Allyl ligands may prevent the formation of the vacant coordination sites necessary for ß-elimination, which enables allylation of tertiary and secondary alkyl halides as well as of alkyl halides having ß-alkoxy groups

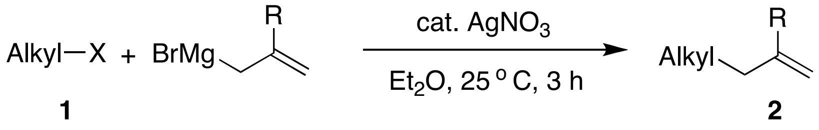
Angew. Chem. Int. Ed. **2002**, 41, 4137

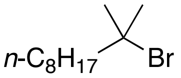
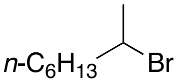
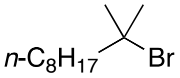
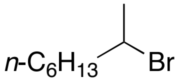
Silver-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Secondary and Tertiary Alkyl Halides

Substrate Scope:



1	cat./mol %	Yield of **2** (%)
	1.0	87
	1.0	66
	1.0	14
	1.0	81



1	cat./mol%	Grignard reagent	Yield of **2** (%)
	1.0	R = H (1.3 equiv)	83
	2.5	R = H (1.3 equiv)	80
	1.0	R = Me (1.5 equiv)	80
	2.5	R = Me (1.5 equiv)	79

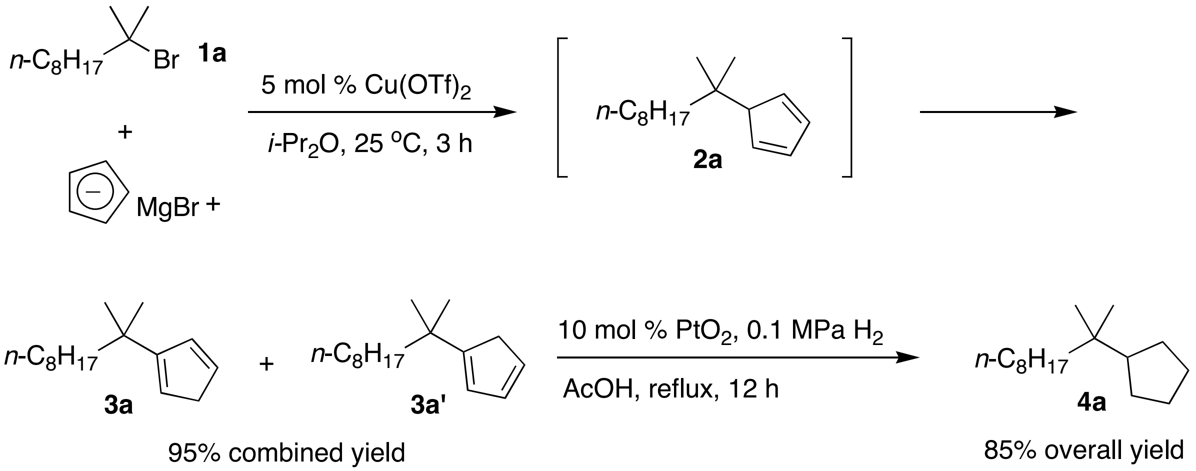
- Silver-catalyzed conditions were applicable to benzylation, as well as allylation and methallylation of secondary and tertiary alkyl halides

- Analogous radical pathway was proposed

Organic Letters **2008**, 10, 971

Copper-Catalyzed Cyclopentadienylation of Secondary and Tertiary Alkyl Halides Followed by Hydrogenation

General Reaction:



-Initially formed **2a** undergoes isomerization into **3a** and **3a’** due to the high acidity of the hydrogen on the cyclopentadienyl ring

- Isomers were subjected to hydrogentation in order to simplify analysis of products

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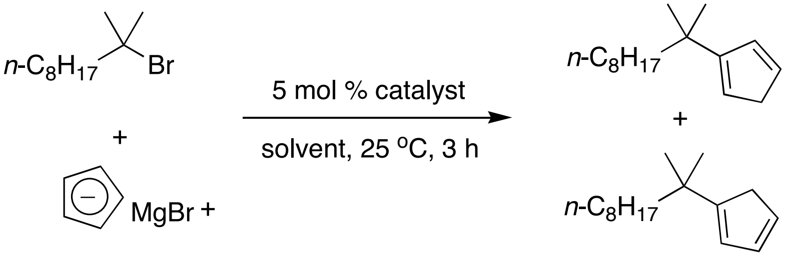
Solvent Effect and Catalyst Screening:



entry	solvent	catalyst	combined yield (%)
1	*i*-Pr_2O	$Cu(OTf)_2$	96
2	*t*-BuOMe	$Cu(OTf)_2$	68
3	toluene	$Cu(OTf)_2$	90
4	diethyl ether	$Cu(OTf)_2$	16
5	dioxane	$Cu(OTf)_2$	12
6	THF	$Cu(OTf)_2$	15
7	*c*-$C_5H_{11}OMe$	$Cu(OTf)_2$	13
8	Bu_2O	$Cu(OTf)_2$	22
9	*i*-Pr_2O	CuF_2	77
10	*i*-Pr_2O	$CuCl_2$	59
11	*i*-Pr_2O	CuCl	44
12	*i*-Pr_2O	CuBr	57
13	*i*-Pr_2O	CuI	31
14	*i*-Pr_2O	CuOAc	30
15	*i*-Pr_2O	CuCN	26
16	*i*-Pr_2O	$CuOTf \cdot 0.5\ C_6H_6$	27
17	*i*-Pr_2O	$AgNO_3$	26

- Choice of solvent and copper catalyst greatly altered overall yield of products

- Bulky ethers (diisopropyl ether and *t*-butyl methyl ether) proved to be most suitable

- Copper(**II**) halides as well as copper(**I**) halides exhibited modest catalytic activity

- Silver(**I**) nitrate, found to be effective in the cross-coupling reaction of tertiary alkyl halides with allyl or benzyl Grignard reagents, was less effective than copper(**II**) triflate

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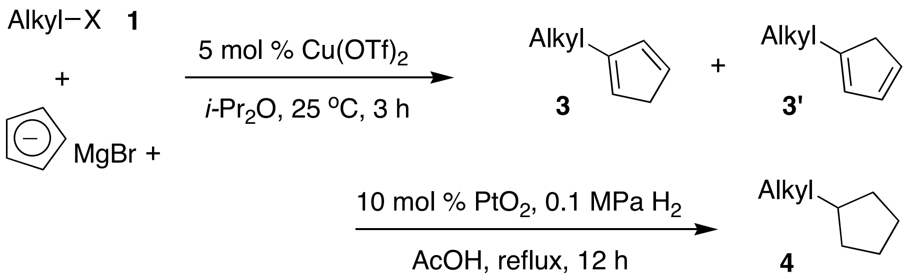
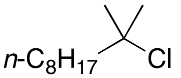
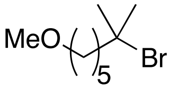
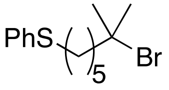
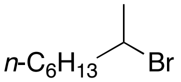
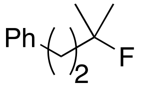
Substrate Scope:



alkyl-X	combined yield of **3** and **3'** (%)	overall yield of **4** from **1** (%)
	88	80
	90	84
	95	50
	51	49
	69	61

- Phenylsulfanyl and methoxyl groups were compatible in such reaction conditions without deactivation of the copper catalyst

- Surprisingly, tertiary alkyl fluoride participated in cyclopentadienylation as well

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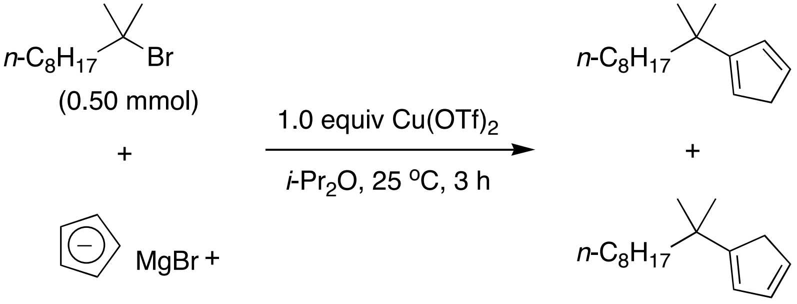
Stoichiometric Reactions:



amount of Grignard reagent	NMR yield
1.0 equiv	0%
2.0 equiv	15%
3.0 equiv	86%

- Reaction mechanism was studied using the following halide with stoichiometric copper reagents and varying amounts of CpMgBr
- Copper reagent that is active for this reaction might be $[Cp_3Cu]MgBr$[6] or a more complex cuprate
- Experiments have been conducted to examine the intermediacy of alkyl radicals in the reaction, however they failed to support the intermediacy

Organic Letters ASAP (4/11/2008)

Conclusions and Future Directions

- Copper(II) triflate proved to efficiently catalyze the reaction of tertiary alkyl halides with cyclopentadienyl Grignard reagent.

- With the following hydrogenation of the cyclopentadienyl ring with hydrogen under Pt_2O catalysis, the overall transformation represents formal cyclopentylation of tertiary alkyl halides.

- Future work could include extension of the methodology to other stabilized organometallic reagents, as well as application of this method to functionalized molecules of interest.