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Catalytic Cross-Coupling of Alkylzinc Halides with α-Chloroketones

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Ketones with multiple substitutents on the α-carbon (α-substituted ketones, **1**) represent important targets for chemical synthesis. The value of this structural motif stems from its prevalence in both natural products and pharmaceutical compounds and from the ability of α-substituted ketones to participate in stereoselective 1,2-additions, olefinations, and enolate reactions. Traditionally, enolate anions have been exploited in the synthesis of α-branched ketones. Thus, deprotonation with a strong base followed by reaction of the resultant enolate with an alkyl electrophile furnishes the substituted ketone (Scheme 1, path a). This strategy has found widespread application,[1] and catalytic variants have been reported.[2] Currently, however, enolate alkylation remains useful primarily for the introduction of sterically unhindered alkyl groups.[3] Additionally, enolate alkylation can be plagued by overalkylation and poor regiocontrol stemming from equilibria between various enolate species.

To address some of the limitations of enolate alkylation, we considered alternative approaches to the synthesis of α-substituted ketones. In particular, we wondered whether α-haloketones could undergo cross-coupling reactions with suitable organometallic reagents (Scheme 1, path b).[4] We report herein the development of a copper-catalyzed reaction of organozinc halides[5] with α-chloroketones.[6] The cross-coupling enables the introduction of primary and secondary alkyl groups adjacent to a ketone carbonyl in high yield and under mild reaction conditions.

Initial efforts to develop the cross-coupling reaction were frustrated by competitive reductive dehalogenation and dimerization of the α-chloroketones. Evaluation of various combinations of organometallic reagents and catalysts led to the discovery that simple Cu(I) and Cu(II) salts catalyze the addition of isopropylzinc chloride to 2-chlorocyclohexanone (**2a**) in excellent yield (Table 1, entries 1−3). Generation of the alkylzinc halide through transmetalation of the Grignard reagent with $ZnCl_2$ proved critical. For example, Mg-free diorganozinc reagents were ineffective (entry 4), although the use of diisopropyl zinc in conjunction with *trans*-1,2-diaminocyclohexane was moderately successful (entry 5). Similarly, organozinc halides obtained from transmetalation of an organolithium reagent or from Zn(0) insertion into an alkyl halide failed to provide any of the desired product (entries 6−7).

The copper-catalyzed cross-coupling of organozinc halides with α-chloroketones tolerates substantial variation in both reacting partners (Table 2). Both cyclic and acyclic α-chloroketones are suitable substrates. Primary, secondary acyclic, and secondary cyclic alkylzinc halides participate similarly well in the cross-coupling reaction. Aryl triflates (entry 20) and aryl nitriles (entry 21) are compatible with the reaction conditions, while *β*-disubstituted α,*β*-unsaturated ketones provide the coupling products in substantially reduced yield.[7]

Scheme 1. Syntheses of α-Substitured Ketones

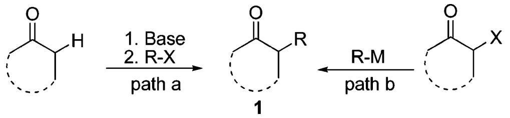
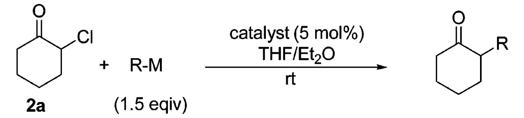


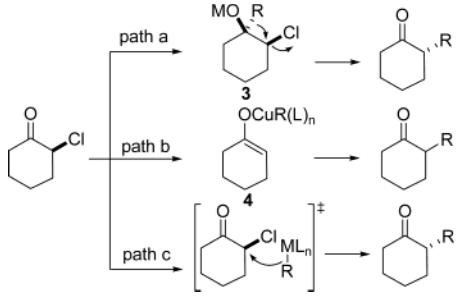
Table 1. Cross-Coupling of **2a** with Organometallic Reagents



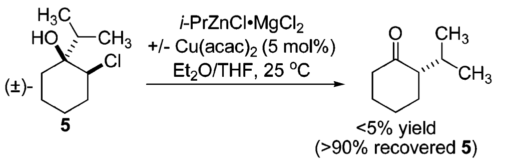
entry	catalyst	R–M	time (h)	yield (%)[a]
1	Cu(acac)$_2$	*i*-PrMgCl+$ZnCl_2$	0.25	>95
2	CuCl	*i*-PrMgCl+$ZnCl_2$	0.25	>95
3	$CuCl_2$	*i*-PrMgCl+$ZnCl_2$	0.25	>95
4	Cu(acac)$_2$	(*i*-Pr)$_2$Zn	1	0[b]
5[c]	Cu(acac)$_2$	(*i*-Pr)$_2$Zn	1	25
6	Cu(acac)$_2$	*n*-C_4H_9Li+$ZnCl_2$	18	0[d]
7	Cu(acac)$_2$	*c*-C_5H_9ZnCl	18	0[e]
8	none	*i*-PrMgCl+$ZnCl_2$	18	21

[a] GC yields relative to an internal standard. [b] 93% conversion of **2a** to unidentified products. [c] 1,2-*trans*-diaminocyclohexane added. [d] >90% recovery of **2a**. [e] 35% conversion of **2a** to unidentified products.

Scheme 2. Potential Reaction Mechanisms



Three different mechanisms could account for the observed cross-coupling. One potential pathway involves 1,2-addition to the ketone followed by 1,2-migration with concurrent loss of Cl^- (Scheme 2, path a). Similar reactivity has been observed with Grignard reagents under forcing conditions.[8] The intermediacy of a tertiary carbinol in the catalytic reaction can be ruled out by the observation that halohydrin **5** is stable to the reaction conditions (eq 1). [9]



(1)

A second potential mechanism for the copper-catalyzed cross-coupling features an alkylcopper enolate (**4**, Scheme 2, path b).[10] Reductive elimination would provide the substituted ketone product as a mixture of stereoisomers. Finally, direct substitution of the alkyl chloride by an organometallic reagent (Scheme 2, path c, M

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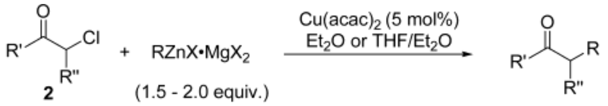
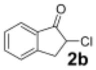
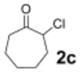
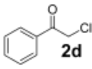
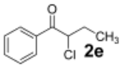
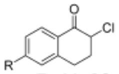
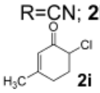
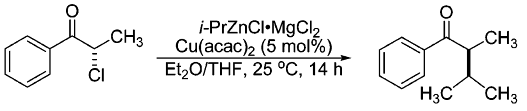
Table 2. Catalytic Synthesis of α-Substituted Ketones[a]



Entry	Ketone	RZnX •MgX$_2$[b]	Solvent	Yield (%)[c]
1	**2a**	*i*-PrMgCl+ZnCl$_2$	THF/Et$_2$O	95
2	**2a**	*n*-C$_4$H$_9$MgCl+ZnBr$_2$	Et$_2$O	85
3	**2a**	*c*-C$_6$H$_{11}$MgCl+ZnCl$_2$	THF/Et$_2$O	96
4	**2a**	*c*-C$_5$H$_9$MgCl+ZnCl$_2$	THF/Et$_2$O	92
5	 **2b**	*i*-PrMgCl+ZnCl$_2$	Et$_2$O	70
6	**2b**	*c*-C$_6$H$_{11}$MgCl+ZnCl$_2$	Et$_2$O	79
7	**2b**	*c*-C$_5$H$_9$MgCl+ZnCl$_2$	Et$_2$O	71
8	 **2c**	*i*-PrMgBr+ZnBr$_2$	Et$_2$O	75
9	**2c**	*c*-C$_6$H$_{11}$MgCl+ZnCl$_2$	THF/Et$_2$O	84
10	**2c**	*c*-C$_5$H$_9$MgCl+ZnBr$_2$	Et$_2$O	75
11	 **2d**	*i*-PrMgCl+ZnCl$_2$	THF/Et$_2$O	90
12	**2d**	*c*-C$_6$H$_{11}$MgCl+ZnCl$_2$	THF/Et$_2$O	90
13	**2d**	*c*-C$_5$H$_9$MgCl+ZnCl$_2$	THF/Et$_2$O	83
14	 **2e**	*i*-PrMgCl+ZnBr$_2$	Et$_2$O	80
				
15	R=H; **2f**	*i*-PrMgCl+ZnCl$_2$	THF/Et$_2$O	89
16	**2f**	*n*-C$_4$H$_9$MgCl+ZnBr$_2$	Et$_2$O	93
17	**2f**	*n*-C$_2$H$_5$MgBr+ZnBr$_2$	Et$_2$O	78
18	**2f**	*c*-C$_6$H$_{11}$MgCl+ZnCl$_2$	Et$_2$O	87
19	**2f**	*c*-C$_5$H$_9$MgCl+ZnCl$_2$	Et$_2$O	85
20	R=OTf; **2g**	*i*-PrMgCl+ZnCl$_2$	THF/Et$_2$O	87
21	R=CN; **2h**	*i*-PrMgCl+ZnCl$_2$	THF/Et$_2$O	82
22	 **2i**	*i*-PrMgCl+ZnBr$_2$	Et$_2$O	45

[a] Reactions were carried out under N_2 for 14 h at 25 °C. See Supporting Information for complete experimental details. [b] Alkyl zinc halide reagents were prepared as suspensions in Et_2O ([RZnX] = 0.2 M) via treatment of ZnX_2 with RMgX. [c] Isolated yields.

= Cu, Zn, or Mg) would occur with inversion of stereochemistry. To distinguish between the latter two mechanistic possibilities, the stereochemical course of the reaction was investigated. Cross-coupling with optically active chloroketone **2j** indicated that the substitution reaction occurs with inversion of stereochemistry (eq 2).[11]



(2)

S-**2j**
95% ee

S-**1ja**
95% ee
77% yield

A final observation pertinent to the mechanistic discussion relates to the reaction of chloroketone **2a** with isopropylzinc chloride in the absence of copper (Table 1, entry 8).[12] This unusual example of an uncatalyzed substitution reaction with an alkyl zinc reagent indicates that a direct displacement pathway is accessible.[5d]

Taken together, the data are most simply explained by a mechanism in which an alkyl group is directly transferred from copper, zinc, or magnesium to the α-carbon of the ketone substrate (Scheme 2, path c). Metal coordination to the chloride or carbonyl may occur, although no evidence currently implicates these modes of activation. The copper-catalyzed substitution of α-chloroketones thus appears mechanistically distinct from copper-catalyzed allylic substitution reactions.[13]

The copper-catalyzed cross-coupling of organozinc halides with α-chloroketones represents a general strategy for the synthesis of α-branched ketones. Furthermore, the use of optically active chloroketones has enabled the preparation of enantiomerically enriched substituted ketones. Notably, the products derived from addition of secondary alkyl zinc reagents would be difficult to access using conventional enolate alkylation. Current efforts are directed toward expanding this reaction manifold to include other classes of nucleophiles and electrophiles.

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Supporting Information Available: Experimental procedures for cross-coupling reactions and eqs 1−2; spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The copper enolate could exist primarily in the η-1 *O*-bound, η-1 *C*-bound or η-3 oxallyl form. For a theoretical study, see: Rosi, M.; Sgamellotti, A.; Floriani, C. *J. Mol. Stuct. (THEOCHEM)* **1999**, *459*, 57−65.
(11) Additional examples can be found in the Supporting Information.
(12) The uncatalyzed reaction occurs with inversion of configuration. See the Supporting Information for details.
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