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Mixed Organocuprates Derived from ortho-Heterosubstituted ArCu Species. Reactions with Simple α,β-Unsaturated Ketones

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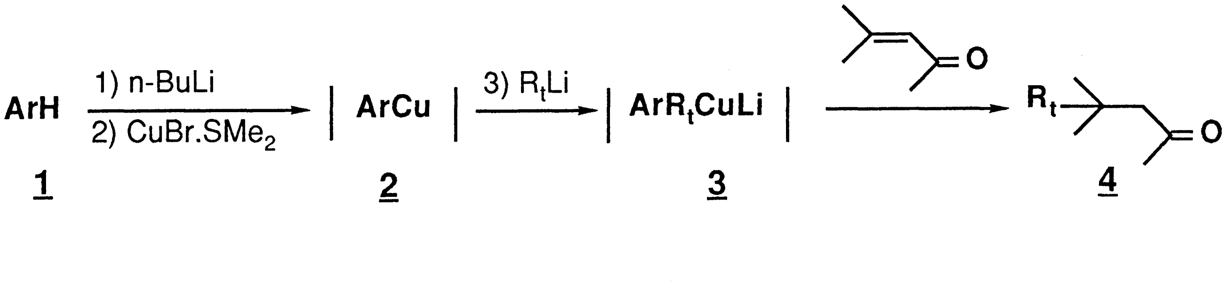
We describe the reaction of new organocuprates of the form ArR_TCuLi (Ar an ortho-heterosubstituted non-transferable ligand), and their reactions with simple α,β-unsaturated ketones.

The addition reactions of organocuprates with α,β-unsaturated ketones have been widely used in organic synthesis for the formation of carbon-carbon bonds.1) Of particular utility are those organocuprates, generally represented as RR_TCuLi, that allow the selective transfer of the ligand of interest, R_T, while the other ligand, R, remains tightly bound to the copper atom during the addition reaction.2) Saegusa and coworkers have shown that the reagent mesityl-Cu can be used to generate useful mixed organocuprates capable of the selective transfer of a variety of R_T, an important exception being bulky groups such as t-Bu.3) As part of a systematic search for useful mixed organocuprates we have investigated the preparation of several mixed organocopper reagents stoichiometrically represented by ArR_TCuLi4) (Ar= non-transferable ligand with ortho heteroatoms relative to copper) and their reactions with simple α,β-unsaturated ketones (equation 1).



The appropriate starting material 1[5] was metallated with n-butyllithium in Et_2O or THF[6] (1-2 h, RT) to form the lithio derivative,[7] which was then allowed to react with $CuBr.SMe_2$ complex (1.1 equiv., 1 h, RT) to achieve the corresponding precursor 2. Cooling of the resulting solution to -80 °C, followed by the dropwise addition of R_TLi (1.1 equiv.) and stirring for 1 h, afforded a solution of the desired mixed cuprate 3 which was treated with neat enone (1 equiv., -80 °C: 1 h, -80 °C ⟶ RT: 1 h). Standard work-up gave the desired saturated ketone 4.

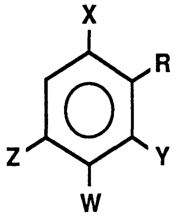
For our initial experiments we chose 1,3,5-trimethoxybenzene (1a) and 2-cyclohexenone, since the first leads to the known ArCu precursor 2a[8] and the latter has been extensively used in conjugated addition reactions. The compound 2a was able to transfer cleanly a wide variety of R_T groups in high yield (R_T= Me, 88%; n-Bu, 89%; t-Bu, 79%; Ph, 93%; H with added HMPA under Saegusa's conditions,[3] 90%). These results encouraged us to study the behavior of similar mixed organocuprates prepared from 2b, 2c, 2d, 2e, and 2f towards 2-cyclohexenone. Table 1 summarizes the general ability of these cuprates to transfer alkyl, vinyl or aryl fragments regioselectively to the β-terminus of the enone, the exception being the mixed cuprate derived from 2d. Particular noteworthy are the high yields of saturated ketone when bulky transferable fragments such as R_T= t-Bu were used. These results suggest that under the reaction conditions employed the heterosubstituted aromatic nucleus remains tightly bound to copper due to coordination-inductive effects of the ortho heteroatoms.

In order to examine the synthetic applications of the new organocuprates, we turned our attention to the possibility of isolating the saturated ketone 4 from the starting material 1, which is also produced during protonation of the reaction mixture. Although conventional chromatography was unable to resolve this problem in a satisfactory way,[9] the desired ketone could be isolated quantitatively by removal of ArOMOM and $ArNMe_2$ co-products by treating the reaction mixture with Dowex cationic resin/MeOH followed by extractive work-up or acid extractive work-up respectively.

The reaction of these organocuprates with more hindered enones such as isophorone and pulegone is considerably slower under the above reaction conditions. In view of this, we studied the selectivity of the addition reaction towards secondary β-centres. Reaction of the representative mixed cuprates

2c-R_TLi or 2e-R_TLi (R_T= n-Bu or t-Bu) with an equimolecular mixture of 2-cyclohexenone and isophorone or pulegone resulted in the quantitative conversion of the former into the corresponding saturated ketone (GLC analysis).

Finally, we have briefly studied the stereochemistry of the addition reaction of two representative mixed organocuprates with 4-methylcyclohexenone under the same reaction conditions. Reaction of 2c-MeLi and 2e-MeLi with this enone afforded 3,4-dimethylcyclohexanone with trans/cis ratios of 15 and 10.8 respectively (100% conversion). The reaction of the corresponding classical homocuprate Me_2CuLi with the same enone afforded 3,4-dimethylcyclohexanone with a slightly lower trans/cis ratios of 9.8.



1, R=H
2, R=Cu

a, X=Y=Z=OMe; W=H
b, X=Y=OMOM; W=Z=H
c, X=Y=Z=OMOM; W=H
d, X=NMe_2; Y=OMe; Z=W=H
e, X=NMe_2; Y=Z=OMe; W=H
f, X=NMe_2; Y=Z=OMe; W=Me

Table 1.[a)]

ArCu	Solvent	Me	n-Bu	t-Bu	$CH=CH_2$	Ph
2a	Et_2O	88	89	79	70	93
2b	THF	80	86	90	60	90
2c	THF	80	100	94	92	92
2d	Et_2O	48	45	60	99	81
2e	Et_2O	91	100	87	82	99
2f	Et_2O	91	94	71	71	95

a) Numbers refer to yields obtained by reaction of ArR_TCuLi with 2-cyclohexenone and were determinated by GLC. The different reaction products were identified by comparison of their ^{1}H-NMR with those of authentic samples.

In conclusion, the above mixed cuprates derived from ortho-heterosubstituted ArCu precursors are able to transfer a wide variety of ligands, including bulky ligands, to non hindered α,β-unsaturated ketones in good to excellent yield. 1e can be recovered in high yield by crystallization after work-up of the reaction mixture. Research continues on reactions of this type of cuprates, including similar chiral derivatives, with α,β-unsaturated carbonyl compounds.

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References

1) For Chemistry related with organocopper reagents, see: B.H. Lipshutz, Synthesis, 325 (1987) and references therein.

2) For non-transferable ligands ("holding groups") that have been successfully used for this purpose, see: C.R. Johnson and D.S. Dhanoa, J. Org. Chem., 52, 1885 (1987) and references therein.

3) T. Tsuda, T. Yazawa, K. Watanabe, T. Fuji, and T. Saegusa, J. Org. Chem., 46, 192 (1981).

4) Although it is known that electronegative ortho heteroatoms in compounds of the type ArCu coordinate with the copper atom (G.J. Lambert, R.P. Duffley, H.C. Dalzell, and R.K. Razdan, J. Org. Chem., 47, 3350 (1982), the influence of such coordination effects in addition reactions of their mixed cuprates have not been studied to date.

5) The ArH used this study were prepared as follows: 1a: Phloroglucinol/K_2CO_3/Me_2SO_4; 1b and 1c: as per C.A. Townsend, S.G. Davis, S.B. Christensen, J.C. Link, and C.P. Lewis, J. Am. Chem. Soc., 103, 6885 (1981); 1d: m-Anisidine/Ac_2O; 1e: 3,5-Dimethoxyaniline/Me_2SO_4/DMF (mp 73-75 °C, satisfactory elemental analysis and spectral data); 1f: 3,5-Dimethoxyaniline/HCHO/$NaBH_3CN$ (mp 81 °C, satisfactory elemental analysis and spectral data).

6) Due to the low solubility of the mixed cuprates derived from 2b and 2c, the reaction had to be conducted in THF.

7) Coordination and inductive effects of ortho heteroatoms allow easy deprotonation of O-hydrogen to the corresponding carbanion. In the case of disubstituted aromatic compounds the metallation occurs at the more hindered position: H.W. Gschwend and H.R. Rodriguez, Org. React., 26, 1 (1979). Deuteration experiments indicate that the metallation of 1e occurs at the ortho (75%) and para (25%) positions. For the metallation of 1b, see: J.J. Talley, J. Org. Chem., 50, 1695 (1985).

8) G.v. Koten, A.J. Leusink, and J.G. Noltes, J. Organomet. Chem., 85, 105 (1975).

9) In exploratory experiments no chromatography separation problems were found in the purification of saturated ketones obtained by reactions of mixed cuprates derived from 2a and higher MW enones such as steroidal α,β-unsaturated ketones.

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