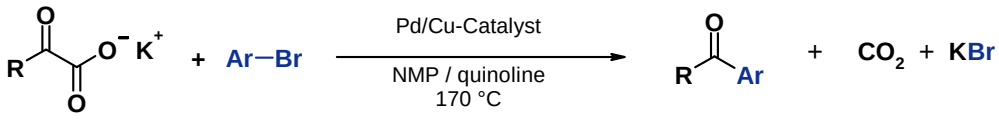
Decarboxylative Cross-Coupling of α-Oxocarboxylates

Lukas J. Gooßen*, F. Rudolphi, N. Rodríguez, C. Oppel

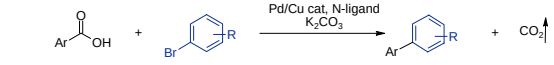
Institut für Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße, 67663 Kaiserslautern,
Tel +49 631 205 2046, goossen@chemie.uni-kl.de

Abstract: We have developed a novel ketone synthesis in which α-ketocarboxylates are decarboxylated at a Cu catalyst, and the resulting acyl anions are coupled with aryl, vinyl or heteroaryl bromides to give the corresponding aryl ketones in excellent yields. This reaction is mediated under relatively mild conditions by a bimetallic catalyst system consisting of CuBr/1,10-phenanthroline and Pd(F_6-acac)/tris-*o*-tolylphosphine. The striking feature of this cross-coupling is that the polarity of the bond formation is inverted compared to traditional ketone syntheses[1,2] from aryl nucleophiles and acyl cation equivalents.



Introduction

Decarboxylation reactions are common in biological systems, generating synthons similar to organometallic reagents in synthetic chemistry. The oxidative decarboxylation of α-oxoglutarate (Krebs cycle) and pyruvate (glycolysis) are the most common examples[3]. We recently introduced this principle to transition metal catalysis and utilized it in a Pd/Cu catalyzed biaryl synthesis from metal benzoates and aryl halides[4]. This reaction is not only intellectually stimulating but also commercially interesting, as the boronic acids, which usually serve as the sources of aryl anions[5] are replaced by inexpensive metal benzoates.

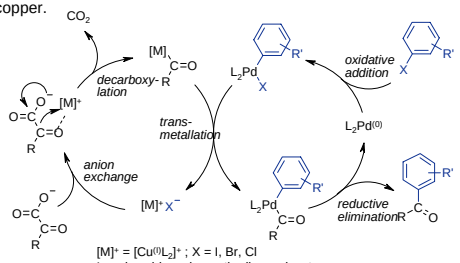


Ar = o-NO_2-C_6H_4, o-CH_3CO-C_6H_4, o-F-C_6H_4, o-H(CO)-C_6H_4, o-MeO-C_6H_4,...

X = Br, Cl
R = Cl, NO_2, $COCH_3$, CN, OCH_3, SCH_3, CHO, CH_3, CF_3,...

α-Ketocarboxylic acids as sources of acyl anions

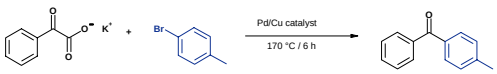
We reasoned that this reaction type may also be extended to α-ketocarboxylic acids as the acyl metal species generated by decarboxylation of these precursors do bear any β-hydrogens and may thus be sufficiently stable to function as intermediates in a cross-coupling reaction.
Our proposed mechanism for such a transformation starts with the decarboxylation of the pyruvate at the Cu-catalyst under the formation of a copper carboxylate. The acyl group then transmetallates to a Pd(II) species generated by the oxidative addition of an aryl halide to a coordinatively unsaturated Pd(0) precursor. The product ketone is released from the Pd-center by reductive elimination, regenerating the palladium catalyst. The copper halide formed during transmetallation exchanges the counterion with fresh potassium pyruvate under formation of copper(I) pyruvate and potassium halide, thus closing a catalytic cycle for copper.



[M]+ = [Cu(I)L_2]+ ; X = I, Br, Cl
L = phosphine, phenanthroline, solvent, ...

Catalyst screening

In order to develop an efficient catalyst system for this desirable transformation, numerous catalysts, ligands and additives were screened for the test reaction of potassium 2-oxophenylacetate with *p*-tolyl bromide, starting from the catalyst that we had successfully employed in our decarboxylative biaryl synthesis[2].



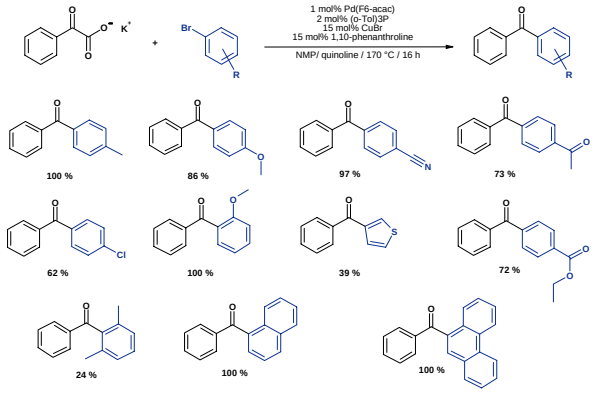
In the screening reactions, 1.2 mmol of the carboxylate were heated with 1.0 mmol of the aryl bromide in 2 ml of an NMP/quinoline mixture (3:1) employing 1 mol% of Pd salts, 15 mol% of Cu salts, 15 mol% of 1,10-phenanthroline, and various ligand and additives. After 6 hours, the reaction turnover was determined by GC using tetradecane as internal standard. A reaction temperature of 170 °C was found to be ideal, as at higher temperatures, thermal decomposition was observed and the reaction was too slow at lower temperatures. The reactions were deliberately stopped at incomplete conversions to best see any effects of altered conditions.

Entry	Pd catalyst	Phosphine	Cu catalyst	Yield (%)
1	$Pd(acac)_2$		CuI	26
2	$PdCl_2$		CuI	29
3	$Pd(F_6\text{-acac})_2$		CuI	31
4	$Pd(acac)_2$		CuOTf	13
5	$Pd(acac)_2$		CuOAc	35
6	$Pd(acac)_2$		CuBr	37
7	$Pd(acac)_2$	PPh_3 (3 mol%)	CuI	31
8	$Pd(acac)_2$	(*o*-Tol)$_3$P (3 mol%)	CuI	42
9	$Pd(F_6\text{-acac})_2$	(*o*-Tol)$_3$P (3 mol%)	CuBr	58
10	$Pd(F_6\text{-acac})_2$	(*o*-Tol)$_3$P (2 mol%)	CuBr	55
11	$Pd(F_6\text{-acac})_2$	(*o*-Tol)$_3$P (2 mol%)	CuBr	100[a]

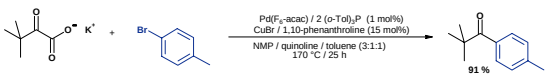
acac = acetylacetonate, F_6-acac= hexafluoroacetylacetonate, OTf = trifluoromethyl sulfonate, (*o*-Tol)$_3$P = tris(*o*-tolyl)phosphine; a) 16 h

Scope with regard to aryl halide

A combination of $Pd(F_6\text{-acac})_2$, (*o*-Tol)$_3$P, CuBr and phenanthroline (entry 11) was finally found to be ideal, as almost quantitative yields were observed in the test reactions with 16 hours reaction time.
In order to probe the generality of the new reaction, we first varied the aryl halide coupling partner and were pleased to find that the reaction appears to be generally applicable to both electron rich and electron poor substrates tolerating a broad range of functional groups. Selected examples are shown below.



The investigation of the scope with regard to the pyruvic acid derivative has just begun, but we are already able to provide exciting results for two rather challenging substrates: The coupling of *p*-tolyl bromide with the electron rich *tert*-butylglyoxylic acid - which should give rise to a particularly destabilized acyl anion - led to the formation of *tert*-butyl *p*-tolyl ketone in more than 90% isolated yield, and the corresponding coupling of the labile 2-thiophenoglyoxylic acid also seems to work.



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