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(F6-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 from aryl nucleophiles and acyl cation equivalents.

Introduction

Decarboxylative reactions are common in biological systems, generating synthons similar to α-ketocarboxylic acids as sources of acyl anions. The oxidative decarboxylation of α-oxoglutarate (Krebs cycle) and pyruvate (glycolysis) are the most common examples1. We recently introduced this principle to transition metal catalysis and utilized it in a Pd/Cu catalyzed biaryl synthesis from metal benzoates and aryl halides4. This reaction is not only intellectually stimulating but also commercially interesting, as the boronic acids, which usually serve as the sources of aryl anions2 are replaced by inexpensive metal benzenes.

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 transmetalates to a Pd(II) species generated by oxidative addition of an aryl halide to a coordinatively unsaturated Pd(II) precursor. The product ketone is released from the Pd-center by reductive elimination, regenerating the palladium catalyst. The copper halide formed during transmetalation exchanges the counterion with fresh potassium pyruvate under formation of copper(I) pyruvate and potassium halide, thus closing a catalytic cycle for copper.

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 o-bromotoluene. Starting from the catalyst that we had successfully employed in our decarboxylative biaryl synthesis2 and screened a variety of organometallic reagents in synthetic chemistry. The oxidative decarboxylation of α-oxoglutarate (Krebs cycle) and pyruvate (glycolysis) are the most common examples1. We recently introduced this principle to transition metal catalysis and utilized it in a Pd/Cu catalyzed biaryl synthesis from metal benzoates and aryl halides4. This reaction is not only intellectually stimulating but also commercially interesting, as the boronic acids, which usually serve as the sources of aryl anions2 are replaced by inexpensive metal benzenes.

Scope with regard to aryl halide

A combination of Pd(F6-acac)2, (o-Tol)3P and CuBr and phenanthroline (entry 11) 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-tolyloctyl 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-thiophenglyoxylic acid also seems to work.

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References: