Cross-Coupling

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Synthesis of Ketones from α-Oxocarboxylates and Aryl Bromides by Cu/Pd-Catalyzed Decarboxylative Cross-Coupling**

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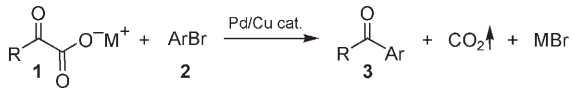
Dedicated to Dr. Nikolaus Müller

Aryl ketones are important structural elements in biologically active compounds and functional materials.[1] Besides Friedel–Crafts acylations,[2] which yield these products mostly as isomeric mixtures, the reaction of activated carboxylic acid derivatives with organometallic reagents,[3] e.g. of Weinreb amides with Grignard compounds, is most often used for their preparation.[4] Transition-metal catalysts increase the efficiency of such cross-couplings such that even carbon nucleophiles of low reactivity, e.g. organozinc compounds and boronic acids, can be converted.[5–7] This results in substantial improvement of functional group tolerance. Reaction variants in which carboxylic acids are activated in situ, such as the palladium-catalyzed synthesis of aryl ketones directly from arylboronic acids and carboxylic acids in the presence of anhydrides[8] or coupling reagents,[9] are particularly convenient.

The reverse approach involving the coupling of acyl anion equivalents with carbon electrophiles is used mainly in the synthesis of alkyl ketones.[10] The required umpolung of the carbonyl function is achieved by the conversion of aldehydes into e.g. cyanohydrins, acetals, dithianes, or hydrazones.[11] In contrast, there are only a few examples of the catalytic arylation of acyl anion equivalents, including the coupling of aryl bromides with *N-tert*-butylhydrazones described by Hartwig et al.[12] Disadvantageous in all reactions of this type are the additional derivatization and hydrolysis steps, as well as the use of strong bases. Arylation of aldehydes by C–H activation offers an atom-economical alternative but has hitherto been possible only with a limited spectrum of expensive aryl iodides.[13]

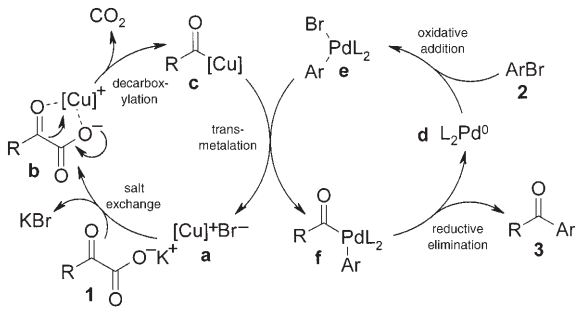
Herein we present a new strategy for the synthesis of aryl ketones in which α-oxocarboxylic acid salts are converted into acyl copper species by decarboxylation on a copper catalyst and then arylated with aryl halides on a palladium catalyst.



Scheme 1. Synthesis of ketones from α-oxocarboxylic acids.

With our synthesis of biaryls from benzoate salts and aryl halides, we demonstrated that decarboxylative cross-couplings can constitute valuable alternatives to the corresponding reactions with organometallic compounds.[14] In subsequent mechanistic investigations of the decarboxylation of benzoic acids[15] we observed that a catalyst system consisting of copper(I) oxide and 1,10-phenanthroline also mediated the decarboxylation of 2-oxophenylacetic acid to benzaldehyde.[16] We conjectured that an acyl anion equivalent was generated at the copper center and protonated to give the aldehyde. Therefore, we decided to carry out this decarboxylation in the absence of protons under basic conditions and combine it with a palladium-mediated cross-coupling with aryl halides to overall afford a decarboxylative ketone synthesis (Scheme 1). The specific advantage of this strategy is that the acyl nucleophiles are prepared in situ, without protecting groups and in the absence of strong bases, from readily accessible and stable salts of α-oxocarboxylic acids.[17]

The hypothetical mechanism of the planned transformation is illustrated in Scheme 2. The potassium α-oxocarboxylate **1** initially reacts with the copper(I) complex **a** by ligand metathesis to form the copper carboxylate **b**. Decarboxylation of **b** affords the acyl copper species **c**, which then transfers its aryl residue to the palladium(II) species **e**, itself derived from the oxidative addition of the aryl halide **2** to the palladium(0) catalyst **d**. The copper(I) halide complex **a** is released in the transmetalation step, closing the catalyst cycle for the copper, while the palladium catalyst **d** is regenerated from the acyl aryl palladium species **f** by reductive elimination of the aryl ketone **3**.



Scheme 2. Postulated catalyst cycle for the aryl ketone synthesis.

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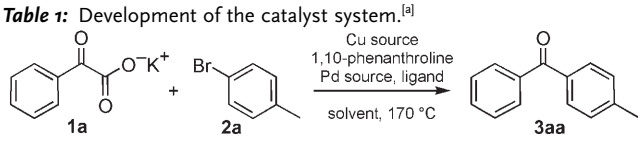
To develop a feasible ketone synthesis based on these mechanistic considerations, we investigated different combinations of copper and palladium catalysts for their efficacy in the test reaction of potassium oxophenylacetate (**1a**) with 4-bromotoluene (**2a**) (Table 1). We were pleased to find that a catalyst system that had already proved to be effective in the decarboxylative biaryl synthesis (15 mol% copper(I) iodide/1,10-phenanthroline and 1 mol% palladium(II) acetylacetonate in *N*-methylpyrrolidone (NMP)/quinoline at 170 °C) afforded modest yields of phenyl 4-tolyl ketone (entry 1, Table 1). The observation that neither copper nor palladium alone were active as catalysts (entries 2 and 3, Table 1) substantiates our proposed reaction path, while alternative mechanisms of the Ullmann or Heck type appear improbable.

Further investigations showed that particularly effective catalysts are formed from copper(I) bromide as the copper source and palladium(II) bis(1,1,1,5,5,5-hexafluoroacetylacetonate), [Pd(F_6-acac)$_2$] as the palladium source (entries 6 and 9, Table 1). The conversion benefits from the addition of phosphane ligands; tris(*o*-tolyl)phosphane (P(*o*-Tol)$_3$) provided the best results (entries 14 and 15, Table 1). This optimized catalyst gave 70% yield after a reaction time of just 6 h and an almost quantitative yield after 16 h (entry 16, Table 1). The stable preformed palladacycle *trans*-di(μ-aceto)bis[*o*-(tolylphosphanyl)benzyl]dipalladium(II) led to results (entry 17, Table 1) comparable to those obtained with the palladium catalyst generated in situ.[18] Of the solvents tested, quinoline and NMP/quinoline mixtures proved particularly suitable. Using pyridine instead of quinoline makes it possible to adjust the reflux temperature to 170 °C, which is particularly useful for larger scale reactions since residual moisture can then be removed continuously by azeotropic distillation.

To ensure that the catalyst system is also suitable for less reactive α-oxocarboxylic acids as substrates, we carried out a number of experiments with potassium 3,3,3-trimethylpyruvate (**1b**). Since even this sterically highly shielded derivative reacted in good yields within 36 h (entry 21, Table 1), we used the optimized catalyst system without modification for the reactions of a variety of aryl bromides with different α-oxocarboxylic acids (Table 2). On the one hand, we found that potassium oxophenylacetate reacted with electron-rich and electron-deficient aryl and heteroaryl bromides to give the phenyl ketones in good yields, and that a wide range of functional groups including esters, ketones, and nitrile groups are tolerated. On the other hand, 4-bromotoluene was likewise coupled in good yields with diverse alkyl-, aryl- and heteroaryl-substituted α-oxocarboxylic acids. The limits of the current catalyst system were reached only with thermally labile (**3ia**, vinylic α-oxocarboxylic acids) and sterically extremely hindered substrates (**3ao**, **3la**).

In summary, this decarboxylative cross-coupling reaction constitutes a single-step synthesis of aryl ketones that is broadly applicable, and unlike conventional ketone syntheses requires no organometallic reagents. Instead, easy-to-handle, readily accessible salts of carboxylic acids, some of which are available on an industrial scale as intermediates in the production of amino acids, are used as source of the acyl nucleophiles. This reaction clearly demonstrates that the concept of decarboxylative cross-couplings is by no means restricted to the synthesis of biaryls but can serve as the basis for the development of a broad spectrum of sustainable cross-coupling reactions. An extension of the decarboxylative couplings to aryl chloride substrates and the reduction of the reaction temperatures by development of more active decarboxylation catalysts are the subject of further investigations.

Table 1: Development of the catalyst system.[a]



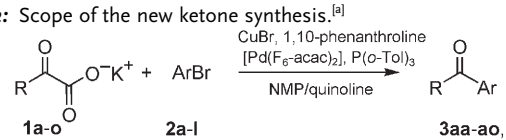
Entry	Cu source	Pd source	Ligand	Solvent	Yield [%]
1	CuI	[Pd(acac)$_2$]	–	NMP/quin.[b]	26
2	CuI	–	–	NMP/quin.[b]	0
3	–	[Pd(acac)$_2$]	–	NMP/quin.[b]	0
4	Cu_2O	[Pd(acac)$_2$]	–	NMP/quin.[b]	20
5	CuOAc	[Pd(acac)$_2$]	–	NMP/quin.[b]	35
6	CuBr	[Pd(acac)$_2$]	–	NMP/quin.[b]	37
7	CuBr	[$Pd_2(dba)_3$][c]	–	NMP/quin.[b]	31
8	CuBr	$PdCl_2$	–	NMP/quin.[b]	34
9	CuBr	[Pd(F_6-acac)$_2$]	–	NMP/quin.[b]	38
10	CuBr	[Pd(F_6-acac)$_2$]	binap[c]	NMP/quin.[b]	26
11	CuBr	[Pd(F_6-acac)$_2$]	PPh_3	NMP/quin.[b]	31
12	CuBr	[Pd(F_6-acac)$_2$]	dppf[c]	NMP/quin.[b]	33
13	CuBr	[Pd(F_6-acac)$_2$]	P(*p*-$MeOC_6H_4$)$_3$	NMP/quin.[b]	62
14	CuBr	[Pd(F_6-acac)$_2$]	P(*o*-Tol)$_3$	NMP/quin.[b]	58
15	CuBr	[Pd(F_6-acac)$_2$]	P(*o*-Tol)$_3$[d]	NMP/quin.[b]	70
16	CuBr	[Pd(F_6-acac)$_2$]	P(*o*-Tol)$_3$[d]	NMP/quin.[b]	99[e]
17	CuBr	[(*o*-Tol)$_2$$PC_7H_6$)Pd(μ-OAc)]$_2$		NMP/quin.[b]	95[e]
18	CuBr	[Pd(F_6-acac)$_2$]	P(*o*-Tol)$_3$[d]	mesitylene/quin.[b]	20[e]
19	CuBr	[Pd(F_6-acac)$_2$]	P(*o*-Tol)$_3$[d]	NMP	56[e]
20	CuBr	[Pd(F_6-acac)$_2$]	P(*o*-Tol)$_3$[d]	quin.	92[e]
21[f]	CuBr	[Pd(F_6-acac)$_2$]	P(*o*-Tol)$_3$[d]	NMP/quin.[b]	90[g]

[a] Reaction conditions: 15 mol% Cu cat., 1 mol% Pd cat., 3 mol% ligand (1.5 mol% with bidentate ligands), 15 mol% 1,10-phenanthroline, 2 mL solvent (quin. = quinoline), 170 °C, 6 h. [b] 3:1 ratio. [c] dba = dibenzylideneacetone, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene. [d] 2 mol% ligand. [e] After 16 h. [f] Potassium 3,3,3-trimethylpyruvate as substrate. [g] After 36 h.

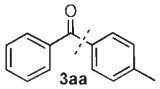
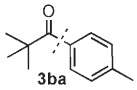
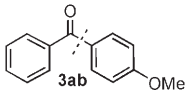
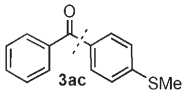
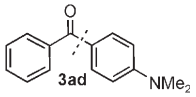
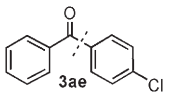
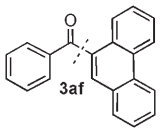
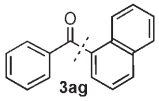
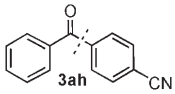
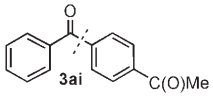
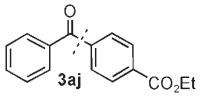
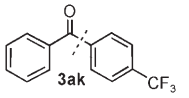
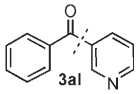
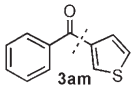
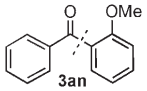
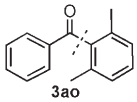
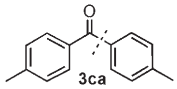
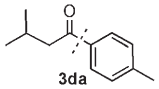
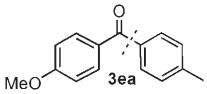
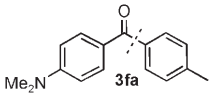
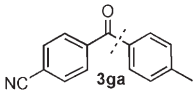
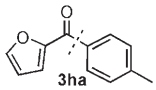
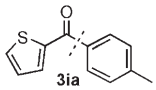
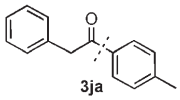
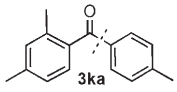
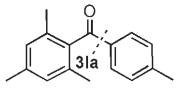
Experimental Section

3ba: A mixture of potassium 3,3,3-trimethylpyruvate (5.05 g, 30.0 mmol), palladium(II) 1,1,1,5,5,5-hexafluoroacetacetonate (104.1 mg, 0.20 mmol), and copper(I) bromide (430.4 mg, 3.00 mmol) under nitrogen was treated with a solution of 4-bromotoluene (3.42 g, 2.46 mL, 20 mmol), tris(*o*-tolyl)phosphane (182.6 mg, 0.6 mmol), and 1,10-phenanthroline (541 mg, 3.0 mmol) in 36 mL NMP and 8.5 mL pyridine with the exclusion of air and moisture. The reaction mixture was heated at reflux (170 °C) for 36 h, cooled, and filtered through Celite, and the filter cake was rinsed with diethyl ether. The filtrate was washed with 1M hydrochloric acid (3 × 20 mL), and the aqueous phases were extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with 100 mL saturated sodium chloride solution, dried over magnesium sulfate, and filtered. After removal of the solvent and Kugelrohr distillation

Table 2: Scope of the new ketone synthesis.[a]



1a-o **2a-l** **3aa-ao, 3aa-la**

Product	Yield [%][a]	Product	Yield [%][b]
 **3aa**	83	 **3ba**	90[c]
 **3ab**	82	 **3ac**	67
 **3ad**	59	 **3ae**	56
 **3af**	83	 **3ag**	82
 **3ah**	99	 **3ai**	78
 **3aj**	70	 **3ak**	72
 **3al**	57	 **3am**	50
 **3an**	73	 **3ao**	26
 **3ca**	72	 **3da**	69[c]
 **3ea**	64	 **3fa**	59
 **3ga**	96	 **3ha**	51
 **3ia**	45	 **3ja**	34[c]
 **3ka**	52	 **3la**	5[d]

[a] Reaction conditions: 15 mol% CuBr, 1 mol% $[Pd(F_6\text{-acac})_2]$, 2 mol% P(*o*-Tol)$_3$, 15 mol% 1,10-phenanthroline, 2 mL NMP/quinoline (3:1), 170°C, 16 h. The substituent originating from the α-oxocarboxylic acid is shown on the left side of the carbonyl group. [b] Yield of isolated product. [c] After 36 h. [d] GC yield.

(105°C/4×10^{-3} mbar), the product **3ba** was obtained as a yellow oil (3.17 g, 90% yield). Its spectroscopic data correspond to those of *tert*-butyl 4-tolyl ketone (CAS 30314-44-4).

The experiments in Table 2 were carried out on a 1.00-mmol scale in 20-mL septum-capped vessels. The products were purified by column chromatography (SiO_2, hexane/ethyl acetate gradient) after aqueous workup.

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Keywords: aryl ketones · copper · cross-coupling · homogeneous catalysis · palladium

[1] a) P. J. Masson, D. Coup, J. Millet, N. L. Brown, *J. Biol. Chem.* **1994**, *270*, 2662–2668; b) K. R. Romines, G. A. Freeman, L. T. Schaller, J. R. Cowan, S. S. Gonzales, J. H. Tidwell, C. W. Andrews, D. K. Stammers, R. J. Hazen, R. G. Ferris, S. A. Short, J. H. Chan, L. R. Boone, *J. Med. Chem.* **2006**, *49*, 727–739.
[2] C. W. Schellhammer in *Methoden der Organischen Chemie (Houben-Weyl)*, *Volume VII/2a* (Ed.: E. Müller), Thieme, Stuttgart, **1973**, p. 15–379.
[3] J. Cason, *J. Am. Chem. Soc.* **1942**, *64*, 1106–1110.
[4] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
[5] E. Negishi, F. Liu in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 18–19.
[6] a) E. Negishi, V. Bagheri, S. Chatterjee, F. T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181–5184; b) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2392–2394.
[7] M. Haddach, J. R. McCarthy, *Tetrahedron Lett.* **1999**, *40*, 3109–3112.
[8] a) L. J. Gooßen, K. Ghosh, *Angew. Chem.* **2001**, *113*, 3566–3568; *Angew. Chem. Int. Ed.* **2001**, *40*, 3458–3460; b) L. J. Gooßen, K. Ghosh, *Eur. J. Org. Chem.* **2002**, 3254–3267; c) L. J. Gooßen, L. Winkel, A. Döhring, K. Ghosh, J. Paetzold, *Synlett* **2002**, 1237–1240.
[9] L. J. Gooßen, K. Ghosh, *Chem. Commun.* **2001**, 2084–2085.
[10] E. J. Corey, D. Seebach, *Angew. Chem.* **1965**, *77*, 1134–1135; *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075–1077.
[11] a) G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **1971**, *93*, 5286–5287; b) R. E. Damon, R. H. Schlessinger, *Tetrahedron Lett.* **1975**, *16*, 4551–4554; c) D. Seebach, *Angew. Chem.* **1969**, *81*, 690–700; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 639–649; d) R. M. Adlington, J. E. Baldwin, J. C. Bottaro, M. W. D. Perry, *J. Chem. Soc. Chem. Commun.* **1983**, 1040–1041.
[12] A. Takemiya, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 14800–14801.
[13] a) Y. C. Huang, K. K. Majumdar, C. H. Cheng, *J. Org. Chem.* **2002**, *67*, 1682–1684; b) S. Ko, B. Kang, S. Chang, *Angew. Chem.* **2005**, *117*, 459–461; *Angew. Chem. Int. Ed.* **2005**, *44*, 455–457.
[14] a) L. J. Gooßen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662–664; b) L. J. Gooßen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824–4833.
[15] L. J. Gooßen, W. R. Thiel, N. Rodríguez, C. Linder, B. Melzer, *Adv. Synth. Catal.* **2007**, *349*, 2241–2246.
[16] Decarboxylation of α-oxocarboxylic acids: a) A. Claus, R. Wollner, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 1856–1861; b) T. Cohen, I. H. Song, *J. Am. Chem. Soc.* **1965**, *87*, 3780–3781.
[17] Synthesis of acylcuprates from organolithium compounds: D. Seyferth, R. C. Hui, *J. Am. Chem. Soc.* **1985**, *107*, 4551–4553.
[18] W. A. Herrmann, C. Brossmer, K. Öfele, C. P. Reisinger, T. Priermeier, M. Beller, H. Fischer, *Angew. Chem.* **1995**, *107*, 1989–1992; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844–1848.

