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Lewis Acid-Promoted Friedel−Crafts Alkylation Reactions with α-Ketophosphate Electrophiles

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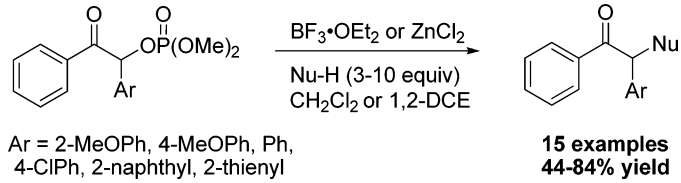
ABSTRACT



The BF_3·OEt_2-promoted nucleophilic substitution of α-aryl-α-ketophosphates to afford α,α-diaryl ketone products is described. Electron-rich α-ketophosphates perform best, with electron-neutral and electron-poor substrates also tolerated. The reaction is tolerant of a range of aromatic, heteroaromatic, and nonaromatic nucleophiles, with yields ranging from 44% to 84%. Enantioenriched starting material yields racemic product, suggesting an S_N1 pathway via an acylcarbenium ion.

α-Aryl carbonyl compounds have garnered considerable attention as synthetic targets, most notably in the chemical production of nonsteroidal anti-inflammatory drugs (NSAIDs). Common drugs such as naproxen, ibuprofen, fluribiprofen, and dichlofenac all contain this moiety.[1] The Pd(0)-catalyzed α-arylation of ketones, pioneered concurrently by Buchwald, Hartwig, and Miura in 1997, has served as the premier route to these products.[2,3] In recent years, this methodology has been expanded to include esters, amides, aldehydes, and lactones as carbonyl coupling partners in the presence of an aryl halide or triflate and a Bronsted base.[4,5]

The aforementioned transition metal-catalyzed routes take advantage of the conventional reactivity patterns of nucleophilic ketone enolates and electrophilic Pd(II) intermediates to arrive at α-arylated carbonyls. We wanted to observe whether formation of an Ar−C_α bond was possible through polarity reversal, or umpolung methodology,[6] with Friedel−Crafts alkylation occurring at an electrophilic α-carbon (Figure 1). Such a route could be envisioned from a substrate

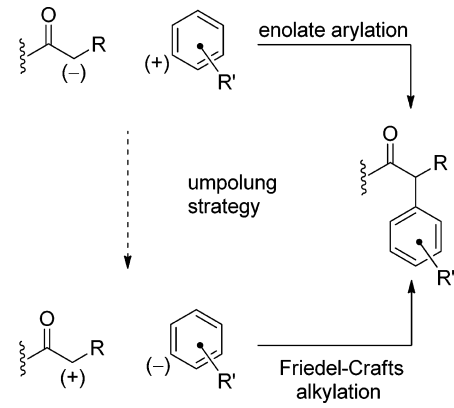


Figure 1. Transition metal-catalyzed enolate arylation (top) and Friedel−Crafts alkylation via an umpolung strategy (bottom).

(1) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953–956.
(2) (a) Hamann, B. C.; Hartwig, J. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740–1742.
(3) For an example of Pd(0)-catalyzed enolate vinylation, see: Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454–3455.
(4) For an α-arylation review, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.

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with a sufficient nucleofuge in place adjacent to the carbonyl functionality (Figure 2).

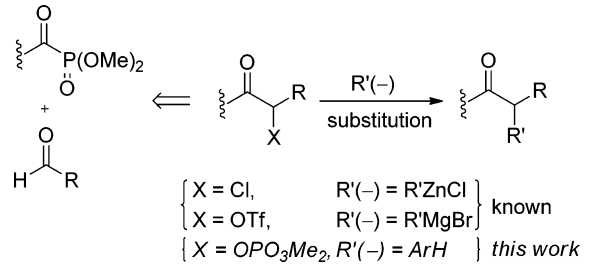


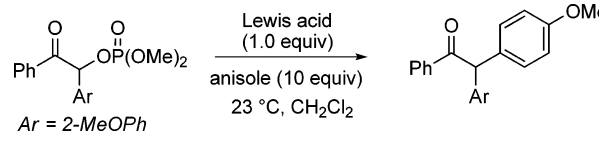
Figure 2. Umpolung approach to α,α-dialkyl carbonyls.

An umpolung α-alkylation route has precedent. In 2004, Ready and Malosh described the copper-catalyzed cross-coupling of primary and secondary organozinc halides with α-chloroketones, providing α-branched ketones in high yields with inversion of configuration at the α-carbon.[7] In 2008, Breit and Studte described a zinc-catalyzed stereospecific sp^3-sp^3 cross-coupling reaction involving alkyl Grignard reagents and α-hydroxy ester triflates.[8] The umpolung alkylation route becomes especially attractive if the needed functionality (i.e., nucleofuge) can be directly installed in conjunction with another synthetic operation. In this context, we noted a potential connection to our previous work demonstrating that cyanide-catalyzed additions of acyl phosphonates to aldehydes provide α-keto phosphate products (Figure 2).[9,10] Acyl phosphonates are easily prepared in one step via the Michaelis−Arbuzov reaction, rendering them a convenient acyl donor. The "phospha-benzoin" reaction forms a C−C bond and installs a potential nucleofuge in a concomitant fashion. In principle, α-substitution reactions are feasible directly on these benzoin products with no prior functional group manipulation required, distinguishing this cross-benzoin route from those conducted with aldehydes, acyl silanes, or benzils as acyl donors.[11,12]

We hypothesized that treating an α-ketophosphate with an appropriate Lewis acid could promote phosphate group ionization and generate an α-acylcarbenium ion that could be subsequently trapped by an arene nucleophile. Such a method would provide a simple route to α,α-diaryl ketones. α-Acylcarbenium ions have been trapped in solution by treating α-halobenzyl ketones with $AgSbF_6$ in the presence of phenol and methanol.[13,14]

We initially tested this reaction design by subjecting α-ketophosphate **1** to a number of readily available and inexpensive Lewis acids in the presence of anisole in CH_2Cl_2 (Table 1). We observed the desired product **2a** regardless of the Lewis acid tried. Performing the reaction at elevated temperatures did not increase the yield for this substrate (entry 5, Table 1). The reaction was catalytic in Lewis acid. Product formation was seen in 59% yield when 10 mol % BF_3•OEt_2 was used (entry 6, Table 1); however, significantly longer reaction times and diminished yields for a number of different substrates led us to examine the reaction scope using a full equivalent of BF_3•OEt_2.

Table 1. Initial Reaction Conditions for the Coupling of α-Ketophosphate **1** with Anisole[a]



entry	Lewis acid	solvent	yield (%)[b]
1	$TiCl_4$	CH_2Cl_2	66
2	BF_3•OEt_2	CH_2Cl_2	67
3	TMSOTf	CH_2Cl_2	66
4	$ZnCl_2$	CH_2Cl_2	66
5[c]	BF_3•OEt_2	CH_2Cl_2	61
6[d]	BF_3•OEt_2	CH_2Cl_2	59
7[e]	BF_3•OEt_2	$CHCl_3$	76
8	BF_3•OEt_2	CCl_4	80
9	BF_3•OEt_2	CH_3CN	71
10	BF_3•OEt_2	$(CH_2)_2Cl_2$	99
11	BF_3•OEt_2	benzene	85
12	BF_3•OEt_2	1,2-DME	74
13	BF_3•OEt_2	toluene	66
14−19[f]	BF_3•OEt_2	[f]	0

[a] Reactions were performed on 0.15 mmol scale, using 1.0 equiv of Lewis acid in CH_2Cl_2 (1.5 mL) at 23 °C for 5 h. [b] Isolated yields obtained after flash chromatography. [c] Reaction performed at 80 °C for 5 h. [d] Reaction performed on 0.15 mmol scale, using 10 mol % catalyst loading. [e] Entries 7−13 were performed on 0.0285 mmol scale, using 100 mol % of BF_3•OEt_2 in the specified solvent (0.29 mL) at 23 °C for 5 h. Yields were calculated by ^{1}H NMR with mesitylene as an internal standard. [f] Entries 14−19: acetone, ^{t}BuOMe, Et_2O, THF, DMF, DMA.

Reaction conditions with different solvents were also explored. Several polar aprotic solvents yielded no desired product, and only α-ketophosphate **1** was recovered (entries 14−19); strongly Lewis basic solvents quelled catalyst reactivity, but the reaction was tolerant of more moderate Lewis bases without competitive Ritter-type reactivity (entry 9). Arene alkylation proceeded in less polar solvents as well as chlorinated solvents, with 1,2-dichloroethane being superior (entry 10).

After initial optimization, we investigated the scope and generality of both nucleophile and α-ketophosphate electro-

(5) For selected examples in synthesis, see: (a) Liu, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182–5191. (b) Martin, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7236–7239. (c) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549–1552. (d) Vo, G. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2127–2130. For alternative methods, see: (e) Milne, J. E.; Murry, J. A.; King, A.; Larsen, R. D. *J. Org. Chem.* **2009**, *74*, 445–447, and references cited therein.

(6) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239–336.

(7) Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 12040–12041.

(8) Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451–5455.

(9) Bausch, C. C.; Johnson, J. S. *Adv. Synth. Catal.* **2005**, *347*, 1207–1211.

(10) Demir, A. S.; Reis, O.; Igdir, A. C.; Esiringu, I.; Eymur, S. *J. Org. Chem.* **2005**, *70*, 10584–10587.

(11) Linghu, X.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833–1840.

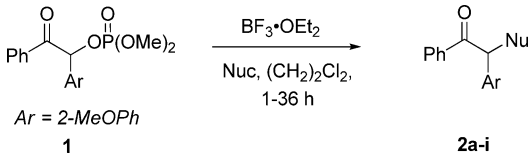
(12) Demir, A. S.; Reis, O. *Tetrahedron* **2004**, *60*, 3803–3811.

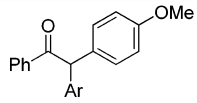
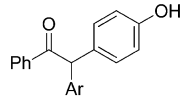
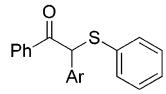
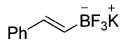
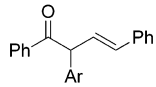
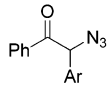
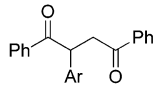
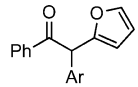
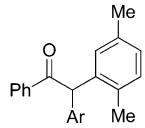
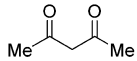
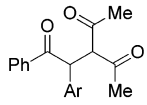
phile in this transformation. Table 2 summarizes the range of nucleophiles employed in this system. Both aromatic and heteroaromatic nucleophiles were tolerated (entries 1−3, 7, and 8, Table 2), with varying reaction times depending on the nucleophile employed. Several nonarene nucleophiles performed well in this system (entries 4−6 and 9). The potassium trifluoroborate styrenyl salt[15] added cleanly in acetonitrile at 90 °C when $ZnCl_2$ was used as the Lewis acid, delivering the trans olefin in 60% yield (entry 4). This reaction allowed for incorporation of a nonaryl sp^2-hybridized carbon center at the α-position. $TMSN_3$ was well-tolerated under the reaction conditions, providing the α-azido ketone in 81% yield (entry 5). Silyl enol ether and acetylacetone addition were also feasible, delivering 1,4-diketone products in promising yields (entries 6 and 9).

Table 3 summarizes the scope of the electrophile with anisole as the nucleophile. Para-substituted aromatic substrates and heteroaromatic substrates were tolerated (entries 1 and 2, Table 3), and the alkylation also progressed in the absence of a strong electron-donating group on the ring (entries 3−5). Heating the reaction to 85 °C allowed for successful ionization of the α-phosphate group in the absence of an electron-donating aryl substituent. Elevated temperatures did result in trace ortho-addition product when anisole was employed as the nucleophile; however, this minor product was easily separated from the para-addition product with silica gel chromatography.

The relatively equal success of a number of Lewis acids (Table 1, entries 1−4) in the initial arene alkylation screen led us to question whether the dialkyl phosphoric acid generated as a byproduct in the reaction was the true promoter of this transformation. To test this, **1** was subjected to a full equivalent of analogous dibutyl phosphoric acid and 10 equivalents of anisole in $(CH_2)_2Cl_2$ (Figure 3). Little

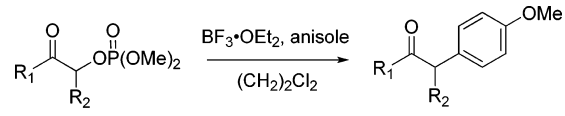
Table 2. Nucleophilic Substitution to **1**[a]



entry	nucleophile	product	yield(%)[b]
1	PhOMe	 **2a**	84
2	PhOH	 **2b**	72
3	PhSH	 **2c**	84
4		 **2d**	60[c]
5[d]	$TMSN_3$	 **2e**	81
6[e]		 **2f**	70
7	furan	 **2g**	83
8[f]	*p*-xylene	 **2h**	44
9[g]		 **2i**	46

[a] Reactions were performed on a 0.29 mmol scale, using 1.0 equiv of BF_3•OEt_2 and 10.0 equiv of nucleophile at 23 °C in $(CH_2)_2Cl_2$ (2.85 mL) unless otherwise noted. [b] Isolated yield after flash chromatography, results averaged over at least two trials. [c] Reaction was performed in CH_3CN (2.85 mL) at 90 °C in a Teflon seal-capped vial, using 1.0 equiv of $ZnCl_2$ and 3.0 equiv of nucleophile. [d] Reaction was performed in CH_2Cl_2 (2.85 mL). [e] Reaction was performed at 80 °C in a Teflon seal-capped vial, using 1.0 equiv of $ZnCl_2$. [f] Reaction performed in CH_2Cl_2. [g] Reaction was performed with 5.0 equiv of nucleophile.

Table 3. Scope of the α-Ketophosphate[a]



entry	R_1	R_2	temp (°C)	time (h)	% yield (product)[b]
1[c]	Ph	4-MeOPh	23	5	73 (**3a**)
2	Ph	2-thienyl	23	1.5	48 (**3b**)
3[d,e]	Ph	2-naphthyl	85	3.5	61 (**3c**)
4[d,f]	Ph	4-ClPh	85	17	51 (**3d**)
5[d,f]	Ph	Ph	85	17	54 (**3e**)
6	4-ClPh	4-MeOPh	23	0.5	71 (**3f**)

[a] Reactions were performed on a 0.29 mmol scale, using 1.0 equiv of BF_3•OEt_2 and 10.0 equiv of anisole in $(CH_2)_2Cl_2$ (2.85 mL) unless otherwise noted. [b] Isolated yield after column chromatography, results averaged over at least two trials. [c] Reaction performed in DCM. [d] Reaction performed in a Teflon seal-capped vial. [e] Ortho-addition product isolated in 7% yield. [f] Ortho-addition product isolated in 8% yield.

(13) Begue, J.-P.; Charpentier-Morize, M. *Acc. Chem. Res.* **1980**, *13*, 207–212.
(14) Kulkarni, G. C.; Karmarkar, S. N.; Kelkar, S. L.; Wadia, M. S. *Tetrahedron* **1988**, *16*, 5189–5198.
(15) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424–8429.

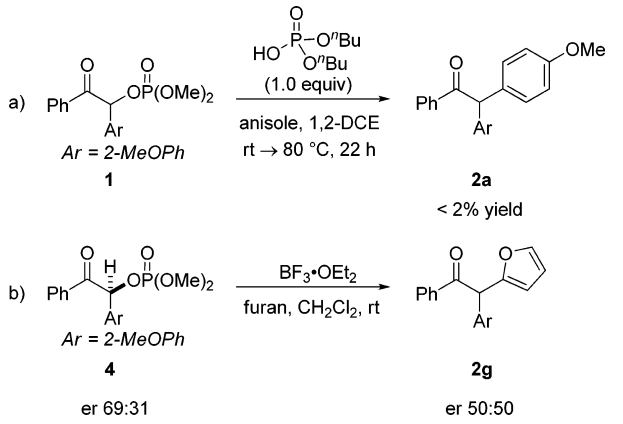


Figure 3. Control experiments: (a) dialkyl phosphoric acid does not promote this reaction; (b) enantioenriched starting material yields racemic product.

desired product was observed upon heating the reaction to 80 °C for 22 h (<2% yield), allowing us to rule out the dialkyl phosphoric acid byproduct as the reaction promoter.

When enantioenriched α-ketophosphate **4**[8] was treated with furan (10 equiv) and BF_3•OEt_2 (1 equiv) in CH_2Cl_2 at 23 °C (Figure 3), the enantiomeric ratio of the resulting product was 50:50, thus suggesting an S_N1 mechanistic pathway that proceeded through a 2° acyl carbenium ion.

In summary, we have discovered a Lewis acid-promoted route to α,α-diaryl ketones that proceeds in one step from an easily prepared α-ketophosphate and invokes an umpolung strategy to induce arene alkylation at the α-carbon. The reaction proceeds at room temperature with sufficiently electron-rich α-ketophosphates; electron-neutral and electron-poor α-ketophosphates react upon heating. The cationic intermediate can be successfully trapped with both heteroatom and nonaromatic nucleophiles. Development of an asymmetric variant of this methodology is currently ongoing in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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