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

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Abstract

The $\text{BF}_3 \cdot \text{OEt}_2$ -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 non-aromatic nucleophiles, with yields ranging from 44-84%. Enantioenriched starting material yields racemic product, suggesting an $\text{S}_{\text{N}}1$ pathway via an acylcarbenium ion.

α -Aryl carbonyl compounds have garnered considerable attention as synthetic targets, most notably in the chemical production of non-steroidal anti-inflammatory drugs (NSAIDs). Common drugs such as naproxen, ibuprofen, flurbiprofen, 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 $\text{Ar}-\text{C}_\alpha$ bond was possible through polarity reversal, or umpolung methodology⁶, with Friedel-Crafts alkylation occurring at an electrophilic α -carbon (Figure 1). Such a route could be envisioned from a substrate with a sufficient nucleofuge in place adjacent to the carbonyl functionality (Figure 2).

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 $\text{sp}^3\text{-sp}^3$ 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.

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

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 AgSbF₆ 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 CH₂Cl₂ (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 % BF₃·OEt₂ 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 BF₃·OEt₂.

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 electrophile in this transformation. Table 2 summarizes the range of nucleophiles employed in this system. Both aromatic and heteroaromatic nucleophiles were tolerated, (entries 1–3, 7–8, Table 2), with varying reaction times depending on the nucleophile employed. Several nonarene nucleophiles performed well in this system (entries 4–6, 9), most notably the potassium trifluoroborate styrenyl salt¹⁵ which added cleanly in acetonitrile at 90 °C when ZnCl₂ was used as the Lewis acid, delivering the *trans* olefin in 60% yield (entry 4). This allowed for incorporation of a non-aryl sp²-hybridized carbon center at the α -position. TMSN₃ 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 (entry 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, when anisole was employed as the nucleophile, did result in trace *ortho*-addition product; however, this minor product was easily separated from the *para*-addition product using 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 by-product 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 (CH₂)₂Cl₂ (Figure 3). Little desired product was observed upon heating the reaction to 80 °C for 22 hours (<2% yield), allowing us to rule out the dialkyl phosphoric acid by-product as the reaction promoter.

When enantioenriched α -ketophosphate **4**⁸ was treated with furan (10 equiv) and BF₃·OEt₂ (1 equiv) in CH₂Cl₂ at 23 °C (Figure 3), the enantiomeric ratio of the resultant 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 non-aromatic nucleophiles. Development of an asymmetric variant of this methodology is currently ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

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

Figure 3.

Control Experiments: a) Dialkyl phosphoric acid does not promote this reaction. b) Enantioenriched starting material yields racemic product.

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 ₂ Cl ₂	66
2	BF ₃ ·OEt ₂	CH ₂ Cl ₂	67
3	TMSOTf	CH ₂ Cl ₂	66
4	ZnCl ₂	CH ₂ Cl ₂	66
5 ^c	BF ₃ ·OEt ₂	CH ₂ Cl ₂	61
6 ^d	BF ₃ ·OEt ₂	CH ₂ Cl 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 ₃ CN	71
10	BF ₃ ·OEt ₂	(CH ₂) ₂ Cl 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	<i>f</i>	0

^a Reactions were performed on 0.15 mmol scale using 1.0 equiv of Lewis acid in CH₂Cl₂ (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 BF₃·OEt₂ in the specified solvent (0.29 mL) at 23 °C for 5 h. Yields were calculated by ¹H NMR with mesitylene as an internal standard.^f entries 14-19: acetone, *t*BuOMe, Et₂O, THF, DMF, DMA.

Table 2

Nucleophilic Substitution to **1**^a

	<div> <p>$\text{Ph}-\text{C}(=\text{O})-\text{C}(\text{Ar})-\text{OP}(\text{OMe})_2$</p><p>$\text{Ar} = 2\text{-MeOPh}$</p><p>1</p></div>	<div>$\text{BF}_3 \cdot \text{OEt}_2$</div> <div>Nuc, (CH₂)₂Cl</div> <div>1-36 h</div>
entry	nucleophile	

1

PhOMe

entry

nucleophile

2

PhOH

Ph

entry

nucleophile

3

PhSH

entry

nucleophile

4

^{5d}TMSN₃

entry

nucleophile

 6^e

entry

nucleophile

7

furan

8f

p-xylene

entry	nucleophile
9 ^g	

^aReactions were performed on a 0.29 mmol scale using 1.0 equiv of $\text{BF}_3 \cdot \text{OEt}_2$ and 10.0 equiv of nucleophile at 23 °C in $(\text{CH}_2)_2\text{Cl}_2$ (2.85 mL) unless otherwise noted.

^bIsolated yield after flash chromatography, results averaged over at least two trials

^cReaction 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.

^dReaction was performed in CH_2Cl_2 (2.85 mL).

^eReaction was performed at 80 °C in a teflon seal-capped vial using 1.0 equiv of ZnCl_2 .

^fReaction performed in CH_2Cl_2 .

^gReaction 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 BF₃·OEt₂ and 10.0 equiv of anisole in (CH₂)₂Cl₂ (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.