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Palladium-Catalyzed β-Arylation of α-Keto Esters

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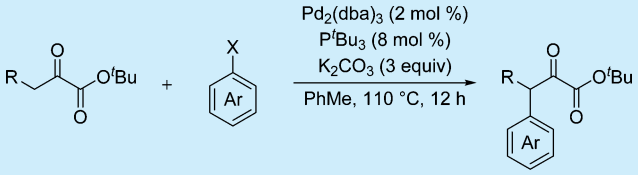
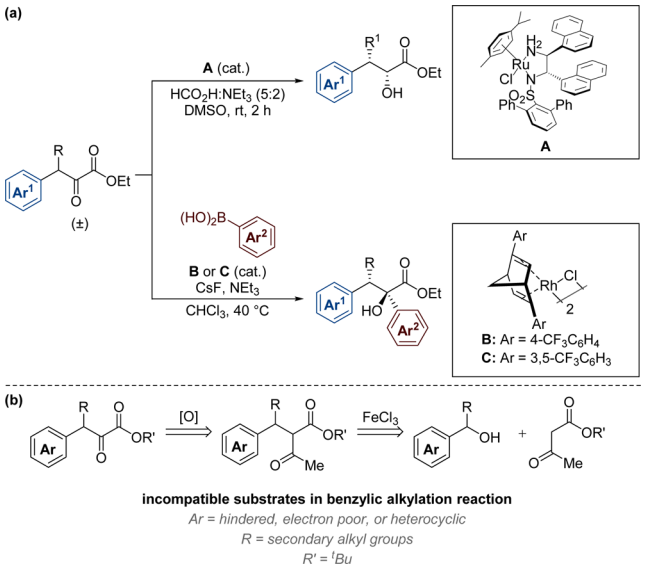
Supporting Information

ABSTRACT: A catalyst system derived from commercially available $Pd_2(dba)_3$ and P^tBu_3 has been applied to the coupling of α-keto ester enolates and aryl bromides. The reaction provides access to an array of β-stereogenic α-keto esters. When the air-stable ligand precursor $P^tBu_3{\cdot}HBF_4$ is employed, the reaction can be carried out without use of a glovebox. The derived products are of broad interest given the prevalence of the α-keto acid substructure in biologically important molecules.



The synthesis of α-keto acids and their derivatives has garnered substantial attention due to their importance in biochemistry[1,2] as well as natural product and bioactive compound synthesis.[3−6] Furthermore, this versatile functional group can serve as a precursor for substituted glycolate products[7−18] and α-amino acid derivatives via the enantioselective transfer hydrogenation of α-imino esters[19,20] or transamination of α-keto esters.[21] Chiral β-aryl α-keto esters are useful electrophiles in dynamic kinetic resolution (DKR) reactions, including Ru-catalyzed asymmetric transfer hydrogenation reactions[12−14] and Rh-catalyzed enantioconvergent arylation reactions (Scheme 1a).[17] These reactions allow for the construction of stereochemically complex glycolate products from racemic starting materials. Unfortunately, current methods to prepare these substrates have some limitations that have hampered efforts to fully explore the scope of these reactions. For example, the sequence of iron chloride, rare Earth metal or hafnium triflate-catalyzed alkylation of active methylene compounds with benzylic alcohols[22,23] and subsequent aerobic deacylation[24] used by our laboratory to access β-aryl α-keto esters has proven to be intolerant of *tert*-butyl esters, bulky β-alkyl substituents, and electron-poor, hindered, or heterocyclic aryl groups (Scheme 1b). While other methods for the synthesis of α-keto esters exist, the scopes of many of these reactions encompass only aryl α-keto esters.[25,26]

Scheme 1. β-Aryl α-Keto Esters: Synthetic Utility and Preparation



To gain entry to a wider array of β-aryl α-keto esters, we considered the development of a palladium-catalyzed α-arylation reaction of *n*-alkyl α-keto esters. Formation of a carbon−carbon bond by utilizing the acidic nature of α-keto esters would constitute an underutilized consonant disconnection of these compounds. Additionally, if successful, this method would allow for a variety of electronically diverse β-aryl α-keto esters to be generated from a single, easily accessible substrate.

Since the first example of a carbonyl enolate arylation reaction, reported in 1973 by Semmelhack and co-workers,[27] the scope of this reaction has been dramatically expanded. The reaction has grown to include the use of ketones, aldehydes, amides, esters, amino acids, nitriles, and activated methylene compounds as substrates.[28−32] We were especially encouraged by the widespread use of tetralones in α-arylation reactions,[33−43] a class of compounds that should have acidities similar to those of α-keto esters. However, *n*-alkyl α-keto esters present a unique set of challenges. A slow reductive elimination from a Pd enolate species could lead to competitive β-hydride elimination.[44] Furthermore, our laboratory and others have observed that α-keto esters with enolizable protons decompose via homoaldol and lactonization in the presence of inorganic bases such as K_2CO_3.[45]

With all of these considerations in mind, we set out to explore the Pd-catalyzed α-arylation reaction of *n*-alkyl α-keto

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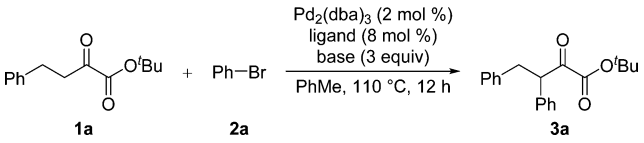
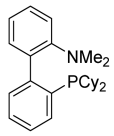
esters. *tert*-Butyl α-keto ester **1a** (Table 1) was chosen as a model substrate to suppress competitive homoaldol addition.[45]

Table 1. Reaction Optimization[a]



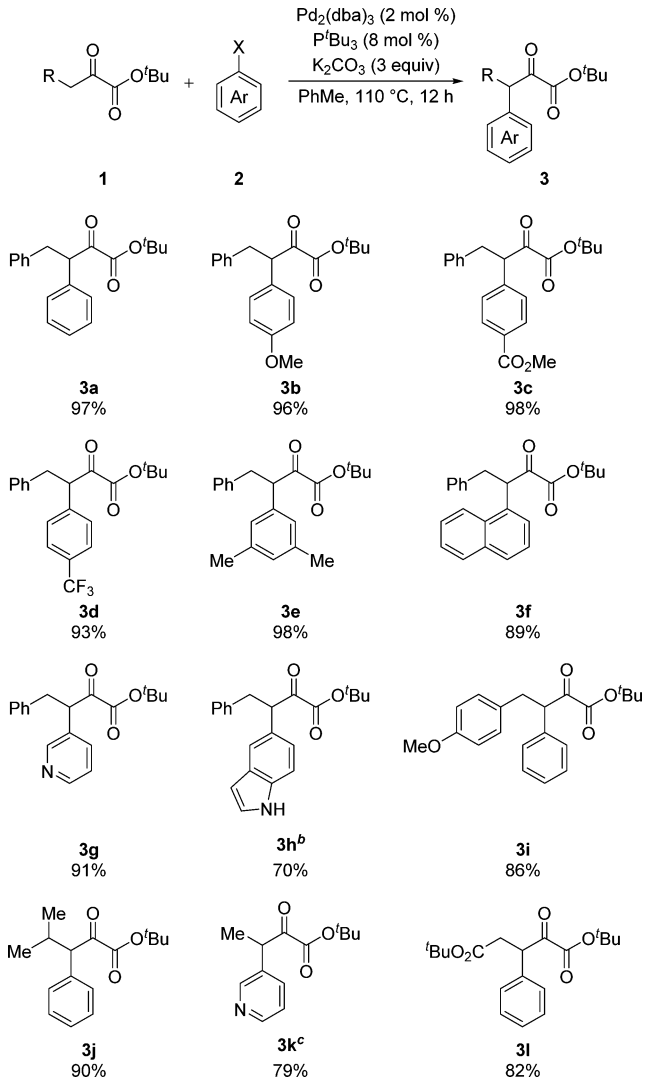
entry	base	ligand	temp (°C)	NMR yield (isolated yield)
1	K_3PO_4	PCy_3	110	< 5
2	K_3PO_4	$PAd_2{}^nBu$ (cataCXium® A)	110	50
3	K_3PO_4	 (DavePhos)	110	43
4	K_3PO_4	P^tBu_3	110	85 (85)
5	KO^tBu	P^tBu_3	110	< 5
6	K_2CO_3	P^tBu_3	110	99 (95)
7[b]	K_2CO_3	P^tBu_3	110	87 (89)

[a]Reaction conditions: 1.0 equiv of **1a**, 2.0 equiv of **2a**, 3.0 equiv of base, 2 mol % of Pd_2dba_3, 8 mol % of ligand, 110 °C, PhMe ($[\mathbf{1a}]_0$ = 0.2 M), 12 h. [b]Reaction conducted with 1 mol % of $Pd_2(dba)_3$ and 4 mol % of P^tBu_3.

We first chose to probe the effect of the supporting ligand, beginning with the electron-rich and sterically hindered ligand tricyclohexylphosphine (entry 1), shown previously to be an effective ligand in Pd-catalyzed enolate arylation reactions.[46] When no appreciable quantity of desired coupled product **3a** was obtained, we moved on to the more sterically encumbered ligand cataCXium A, which delivered keto ester **3a** in reasonable yield (entry 2). Encouraged by this result, we switched to the Buchwald-type ligand DavePhos (entry 3), which is also well-precedented to work in this type of reaction.[47] When a slight decrease in yield was observed, we took inspiration from Hartwig's arylation of malonate derivatives,[48] employing tri-*tert*-butylphosphine. This ligand provided product **3a** in an isolated yield of 85% (entry 4). The disparity between this isolated yield and the pristine ^1H NMR spectrum of the crude reaction mixture led us to believe that some base-promoted decomposition to intractable materials was occurring. Taking this into consideration, we sought to find a more optimal base and found that the less basic potassium carbonate improved the isolated yield of the reaction to 95% (entry 6). Notably, product **3a** was still formed in high yield when 2 mol % of palladium was employed. (1 mol % of $Pd_2(dba)_3$, entry 7).

With optimal conditions in hand, we next turned to analyzing the scope of the Pd-catalyzed cross-coupling reaction (Scheme 2). First, a variety of aryl bromides were tested. Both electron-rich and electron-poor aryl groups gave excellent results. For instance, α-keto esters **3c** and **3d**, which would have been difficult compounds to access using our previous routes (vide supra), were obtained in excellent yields. The reaction also

Scheme 2. Scope of α-Keto Ester Enolate Arylation Reaction[a]



[a]Reaction conditions: 1.0 equiv of **1**, 2.0 equiv of **2**, 3.0 equiv of K_2CO_3, 2 mol % of Pd_2dba_3, 8 mol % of P^tBu_3, PhMe ($[\mathbf{1}]_0$ = 0.2 M), 110 °C, 12 h. [b]Reaction gave 69% yield when scale was increased to 2.7 mmol. [c]Reaction conducted on 1 g scale.

tolerated various types of aryl groups allowing the synthesis of products with *meta* substituents (**3e**) and *ortho* substituents (**3f**). Of particular interest to us was the use of heterocyclic aryl bromides. We were pleased to find that 3-bromopyridine and unprotected 5-bromoindole proved to be viable coupling partners (**3g** and **3h**). The use of alkenyl halides resulted in decomposition of the starting materials (not shown). In addition to the parent substrate **1a**, other α-keto esters were evaluated in the enolate arylation reaction. As seen with product **3j**, this method allowed facile entry to α-keto esters with bulky β-alkyl substituents. Additionally, decreasing the size of the β-alkyl substituent did not significantly decrease the yields (**3k**). Finally, in order to test the chemoselectivity of this reaction, a substrate containing both an ester and an α-keto ester was tested. Product **3l** was generated without any noticeable formation of a bis-arylated product, highlighting the gentle nature of these reaction conditions. When β-disubstituted α-keto esters were used in this reaction,

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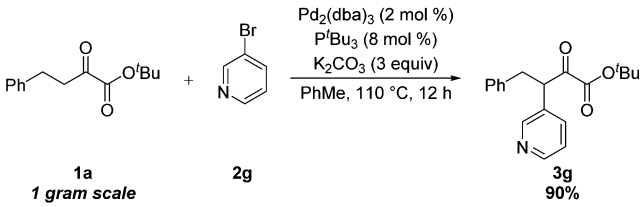
decomposition of the starting materials and low conversion to the tertiary β-substituted product was observed (not shown).

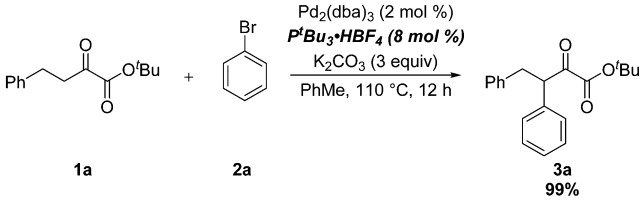
The syntheses of products **3k** (Scheme 2) and **3g** (Scheme 3) were accomplished on a 1-g scale with yields almost identical

Scheme 3. Practical Considerations Associated with the Title Reaction

(a) Gram Scale Reaction



(b) Reaction Set up Outisde of a Glovebox[a]



[a] $Pd_2(dba)_3$, $P^tBu_3{\cdot}HBF_4$, K_2CO_3, and PhMe were mixed for 2 h prior to addition of **1a** and **2a**. See the Supporting Information for full experimental details.

to those obtained in experiments on a smaller scale. Furthermore, the reaction could be carried out without the use of a glovebox when $P^tBu_3{\cdot}HBF_4$ was used in place of the air-sensitive P^tBu_3 (Scheme 2b).[49] The latter can be synthesized in house from cheap starting materials.[50]

In conclusion, we have developed a Pd-catalyzed β-arylation reaction of α-keto esters that allows for the generation of a wide array of aryl pyruvate derivatives. These reactions typically proceed in excellent yield and provide access to previously inaccessible β-heteroaryl derivatives. Finally, the reaction can be conducted without the use of a glovebox.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00761.

Experimental procedures, characterization data for all new compounds, and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds reported in the text (PDF)

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Notes

The authors declare no competing financial interest.

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